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GOLD CATALYSIS AND ITS APPLICATIONS IN SYNTHESIS OF  
FLUORINATED ORGANIC COMPOUNDS

By

Weibo Wang

A Dissertation  
Submitted to the Faculty of the  
College of Arts and Sciences of the University of Louisville  
in Partial Fulfillment of the Requirements  
for the Degree of

Doctor of Philosophy

Department of Chemistry  
University of Louisville  
Louisville, Kentucky

December, 2011

# GOLD CATALYSIS AND ITS APPLICATIONS IN SYNTHESIS OF FLUORINATED ORGANIC COMPOUNDS

By

Weibo Wang

A Dissertation Approved on

December. 7<sup>th</sup>, 2011

by the following Dissertation Committee:

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Dr. Xiang Zhang

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Dr. Gary A. Cobbs

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# ABSTRACT

## GOLD CATALYSIS AND ITS APPLICATIONS IN SYNTHESIS OF FLUORINATED ORGANIC COMPOUNDS

Weibo Wang

December, 2011

Our research activities are based on the catalytic systems that provide resource-saving synthetic methodologies through gold-catalyzed reactions of alkynes and alkenes. We have worked on three applications: i) an effective and straightforward hydration of 3-alkynoates catalyzed by gold (III); this mild and atom-economical method can be used effectively with a wide range of substrates with high regioselectivity; ii) an efficient monofluorination of allyl silanes using Selectfluor has been achieved without gold catalysts; iii) a fluorine-enabled cationic metal species, generated by fluorination of a low valence gold(I) complex, catalyzed the hydration of alkynes to give  $\alpha$ -substituted- $\alpha$ -fluoroketones in one pot under mild conditions. The latter allowed a diverse range of fluorine building blocks or targets to be made available using tools that are amenable in combinatorial or parallel synthesis conditions in drug discovery laboratories or process chemistry.

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# CHAPTER 1. INTRODUCTION

## 1.1 Background of gold catalysis

The element of gold has been studied from the early days of human history, but it has found little use in chemical synthesis until recently. During the last 15 years or so, there has been an impressive focus on the utility of gold catalysis in organic synthesis.<sup>1-8</sup> Gold catalysis is considered as more environmentally benign and a resource-saving synthetic methodology for the synthesis of numerous target molecules.<sup>9</sup> From a green chemistry standpoint, gold catalysts have clear advantages: reactions often proceed under room temperature within short time.<sup>10</sup> Furthermore, gold catalysts can tolerate air and moisture environments.<sup>3</sup>

### 1.1.1 Features of gold catalysis

**Strong  $\pi$ -acidity:** Cationic gold is a soft Lewis acid, with a large radius, low or partial ( $\Delta+$ ) positive charge. Electrons in its valence shell are easy to polarize. Because of the  $\pi$ -acidity, gold is considered an alkynophilic Lewis acid. A lower LUMO and the poor electron back donation of gold make it the most powerful catalyst for electrophilic activation of alkynes toward a variety of nucleophiles.

**Both Au<sup>I</sup> and Au<sup>III</sup> are active in catalysis:** Of the different oxidation states of gold, gold(0), gold(I), and gold(III) are the main ones. In an aqueous solution without any ligand, gold(I) spontaneously disproportionates to gold(III) and gold(0).<sup>1</sup> In contrast to tricoordinated and tetracoordinated Cu(I) and Ag(I) complexes, Au<sup>I</sup> ( $d^{10}$ ) has a linear bicoordinate geometry, this fact makes it difficult to be used in asymmetric catalysis. Gold<sup>III</sup> ( $d^8$ ) complexes are four-coordinated (square planar) and diamagnetic. When the formal coordination number is less than 4, ligands such as chlorine can make up for it by forming a bridging ligand. Cationic gold (III) complexes are generally considered stronger catalysts than gold (I).

**No  $\beta$ -H elimination:** In contrast to other transition metal complexes (e.g. Pd), organogold complexes have a low tendency to undergo  $\beta$ -H elimination; Au-H complexes are rare.

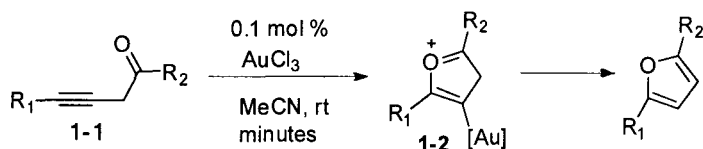
### 1.1.2 Typical gold catalyzed reactions

#### A. Simple nucleophilic additions to C-C multiple bonds

This is by far the most common reaction pattern in gold catalyzed organic reactions. Gold activates the C-C bonds of alkynes, allene, or olefins toward attack by nucleophiles.

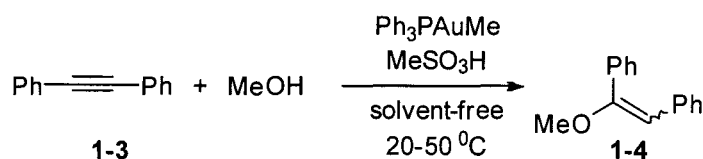
**Alkynes as substrates:** One typical example is shown in Scheme 1. Hashmi et al.<sup>11</sup> initially found that gold (III) can complete the cycloisomerization of propargyl

ketone **1-1** by nucleophilic attack of the carbonyl group, followed by aromatization of the intermediate arenium ion **1-2** to furan (Scheme 1).



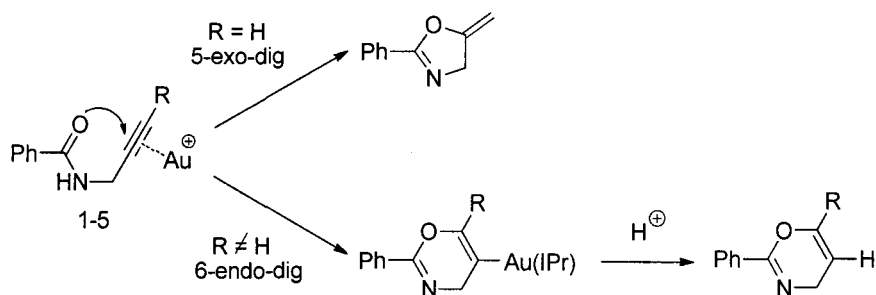
**Scheme 1. Cycloisomerization of propargyl ketone.**

In 1998, Teles et al.<sup>12</sup> found very high activities, TON (turnover number) up to  $10^5$ , and TOF (turnover frequency) up to  $5400 \text{ h}^{-1}$  for cationic gold (I) phosphine complexes in the addition of alcohols to alkynes. This type of cationic complex is still the most homogeneous gold catalyst. Indeed, the  $\text{Ph}_3\text{PAu}^+\text{X}^-$  system has been used by many of the authors cited in this chapter. The following example, shown in Scheme 2, depicts the reaction of biphenyl acetylene **1-3** by which methanol attacks the alkyne that has been activated by cationic gold  $\text{Ph}_3\text{PAu}^+$  (generated *in situ* by reaction of  $\text{Ph}_3\text{PAuMe}$  with the acidic promoters) to produce the (Z)-isomer **1-4**.



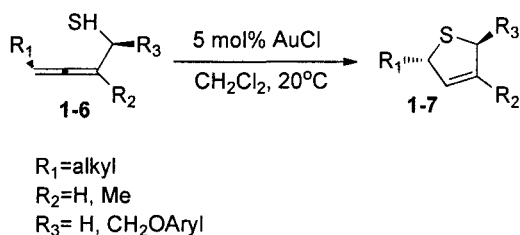
**Scheme 2. Reaction of biphenyl acetylene.**

In 2004, Hashmi<sup>13</sup> reported the use of N-propargyl carboxamides **1-5** having alkynyl groups (Scheme 3,  $\text{R}=\text{H}$ ) for 5- exo-dig cyclizations, and in 2009, they<sup>14</sup> reported the 6-endo-dig cyclization of N-propargyl carboxamides **1-5** possessing an internal alkynyl group (Scheme 3,  $\text{R}\neq\text{H}$ ) .



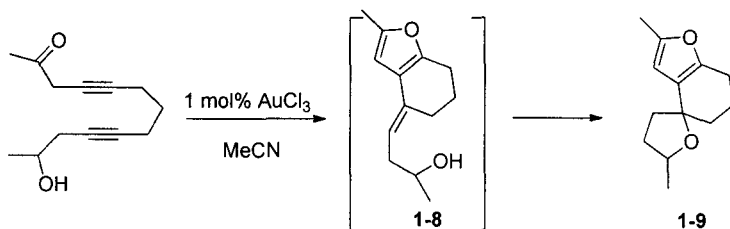
**Scheme 3. Cyclization of N-propargyl carboxamides.**

**Allenes as Substrates :** Krause et al. used allenyl thiocarbinols **1-6** as substrates<sup>15</sup> in the cyclization to 2,5- dihydrothiophenes **1-7** (Scheme 4); the best results were obtained with AuCl in CH<sub>2</sub>Cl<sub>2</sub>.



**Scheme 4. Cyclization of allenyl thiocarbinols.**

**Alkenes as Substrates :** In 2000, Hashmi<sup>11</sup> et al. reported the first gold–catalyzed intramolecular addition of a hydroxy group to an activated alkene **1-8** to form spirocycle **1-9** ( Scheme 5) .



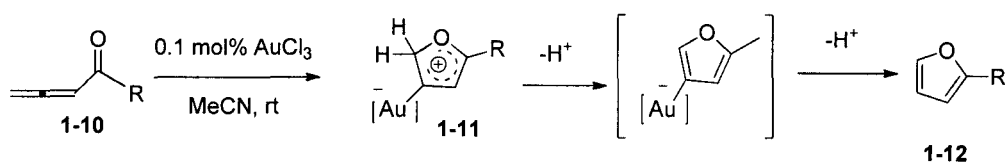
**Scheme 5. Hydroarylation of alkene.**

## **B. Intramolecular additions in conjugated $\pi$ - systems and related reactions**

In these intramolecular reactions, the nucleophilic group is in conjugation with the double bond, which is activated by the gold catalyst. In most cases, this



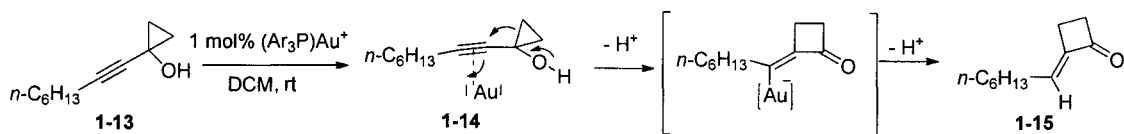
ultimately leads to conjugated (aromatic) products. For example, the cycloisomerization of allenyl ketones **1-10** has been reported by Hashmi<sup>11</sup> et al. The carbonyl oxygen atom serves as an intramolecular nucleophile, the Wheland-type intermediate **1-11** then delivers the product **1-12** by aromatization to **1-11** via proton loss and subsequent protodeauration (Scheme 6).



**Scheme 6. Cycloisomerization of allenyl ketones.**

### C. Ring enlargement reactions

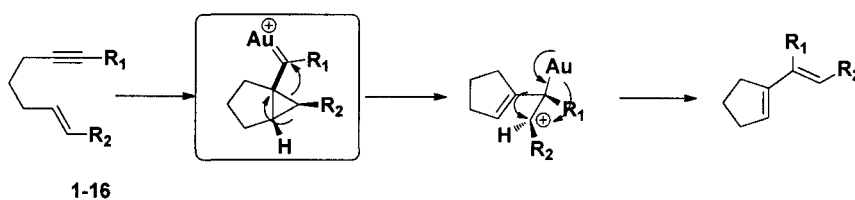
In 2005, Toste<sup>16</sup> et al. reported the ring expansion of ethynyl cyclopropanols **1-13** (Scheme 7). Here, the strained ring in **1-14** forms a bond with the proximal carbon of the alkyne and not with the distal one and the proton of the hydroxyl group is eliminated to give the ketone product **1-15**.



**Scheme 7. Ring expansion of ethynyl cyclopropanols.**

### D. Cycloisomerization of enyne

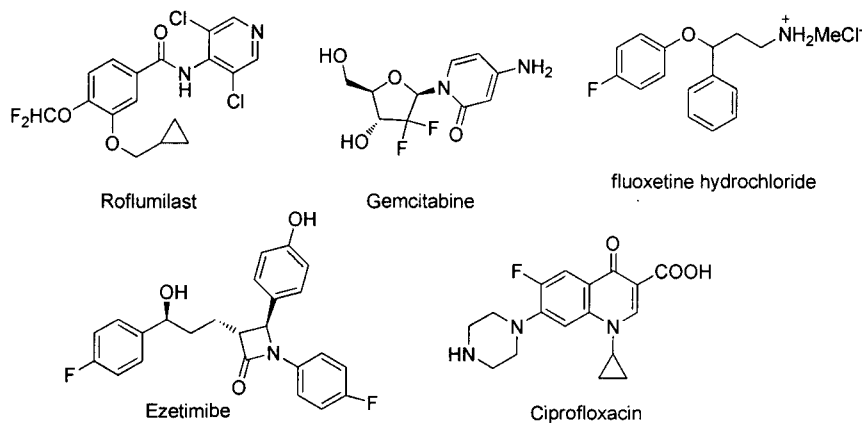
Metal-catalyzed cyclizations of enyne **1-16** have been reported by Echavarren<sup>17</sup> in 2006: the Au catalyst selectively activates the alkyne followed by an anti attack of the alkene (Scheme 8).



**Scheme 8.** Cycloisomerization of enyne.

## 1.2 Fluorine chemistry

Extensive research has established that the chemical reactivity of fluorinated organic compounds is distinctly different from other halide-containing analogues.<sup>18-24</sup> The small size of fluorine, its high electro negativity, and its strong bond with carbon, contribute to the fact that, once fluorine is introduced into an organic compound—either in place of a hydrogen atom or another organic functionality—induces only minimal steric alterations but profound electronic changes in the resulting compound. Consequently, fluorine substitution can effectively modify the physical-chemical properties of the molecule.<sup>18-24</sup> Until 1957, though, no F-containing drugs had been developed. These days, fluorinated drugs make up 20% of all pharmaceuticals sold worldwide, with even higher figures for agrochemicals (Figure 1).



**Figure 1.** Examples of therapeutic drugs containing fluorine.

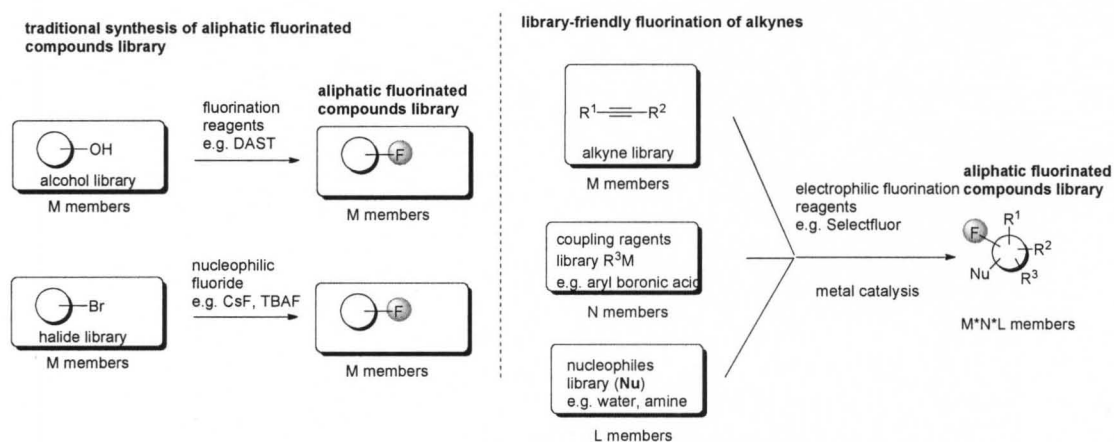
Compared with other heteroatom, It is not easy to introduce fluorine into an organic compound, especially in non-aromatic systems. Today, the synthesis of drugs and agrochemicals rely on commercially available stocks of fluorinated aromatic substrates (e.g. fluorine-substituted benzaldehydes). Fluoroaromatics can be made by traditional methods like conversion of aromatic amines via the aryldiazonium salt (Balz-Schiemann reaction)<sup>25</sup> and the nucleophilic substitution of electron-poor bromo- or chloroarenes with KF (Halex reaction)<sup>26</sup> as well as the more recent transition-metal promoted Ar-F bond formation with electrophilic "F<sup>+</sup>" reagents such as Selectfluor or N-fluoropyridinium salts.<sup>27-29</sup> By far, the most common method that medicinal chemists use to make aliphatic fluorinated compounds is through the conversion of alcohol, carbonyl compounds or alkyl halides to fluorinated compounds by fluorination (e.g., DAST).<sup>20</sup> But this protocol is not library-friendly, each fluorinated product need one specific starting material (Figure 2, left). Because of this, fluorine is not a user-friendly substituent to introduce, especially when it comes to generate synthetic libraries using combinatorial tools, so it comes as no surprise that the number of drug candidates possessing aliphatic or cyclic fluorine substituent is so dismally low.

## **1.3 Gold catalysis meet fluorine chemistry**

### **1.3.1 Library-friendly synthesis of aliphatic fluorinated compounds**

We propose here a more efficient strategy to access aliphatic fluorocompounds, using fluorine-generated cationic metal species to mediate a tandem nucleophilic addition /coupling/fluorinations reaction, starting from readily available alkynes. One advantage of alkynes is that they are ubiquitous in synthesis and many of

them are commercially available.<sup>30,31</sup> Their reaction with suitable coupling reagents (e.g. phenyl boronic acid) and suitable nucleophiles (e.g. water, amine, malonate) in the presence of fluorination reagents (e.g. Selectfluor) will generate a diversified library of aliphatic fluorinated compounds ( $M*N*L$  members, Figure 2, right). An additional advantage is that alkynes are chemically inert to many reaction conditions (like acidic or basic conditions); which is especially important when using alkyne intermediates in late steps of target syntheses.

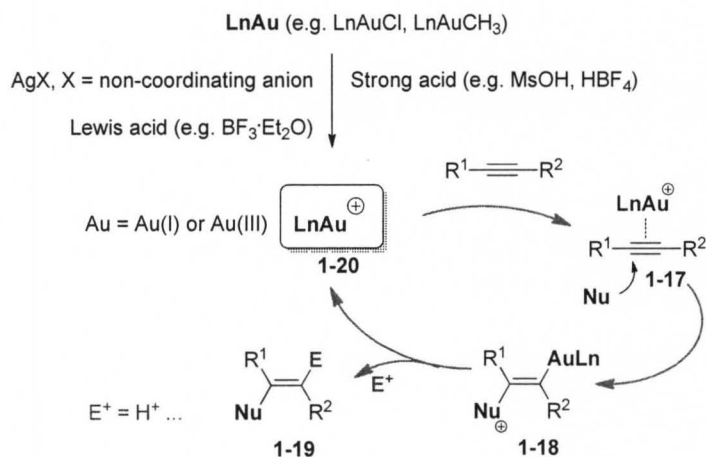


**Figure 2. Library-friendly synthesis of aliphatic fluorinated compounds library.**

### 1.3.2 General transition metal catalytic cycle

Transition metal catalysts play a major role in chemical synthesis.<sup>32</sup> Many transition metals need to be cationic form to be catalytically active; a case in point is gold.<sup>1,3,4,6</sup> Cationic gold salts have been regarded as the most powerful catalysts for electrophilic activation of alkynes toward a variety of nucleophiles.<sup>1,3-8,33</sup> Put simply, a nucleophilic attack on a  $[AuL]^+$ -activated alkyne **1-17** proceeds via a  $\pi$ -complex to give a *trans*-alkenyl gold complex intermediate **1-18** capable of reacting with an electrophile ( $E^+$ )--normally proton, to yield the final product **1-19** through protodeauration (Scheme 9). A common gold catalyst precursor, such

as  $\text{Ph}_3\text{PAuCl}$ , is not catalytically active by itself. It is typically treated with a silver salt of a non-coordinating anion to generate the active cationic gold complex **1-20** (Scheme 9).

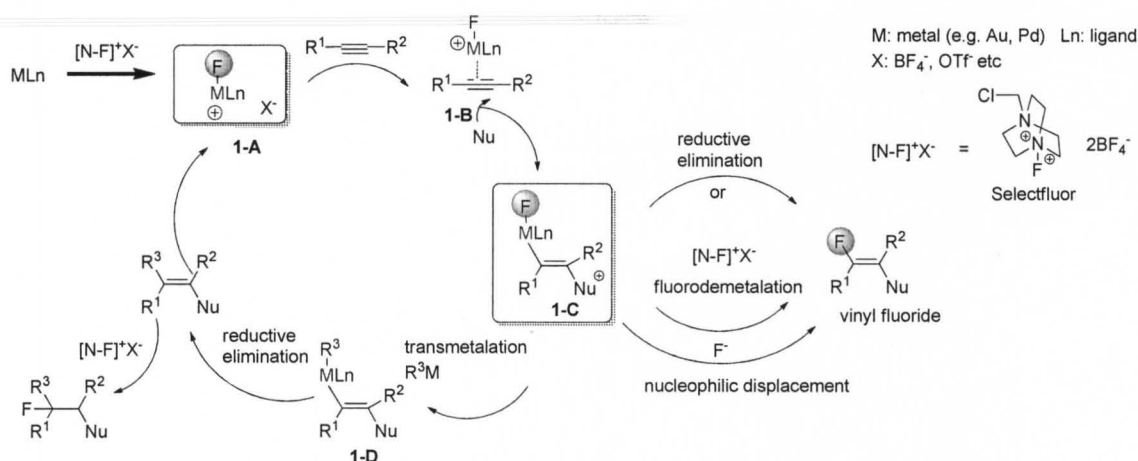


**Scheme 9. Traditional methods for generation of  $[\text{LnAu}]^+$  and its catalytic cycle.**

### 1.3.3 Fluorine-engendered cationic transition metal species.

We envision a new mode of catalysis through a fluorine-enabled cationic metal species generated by fluorination of a low valence metal complex (e.g.  $\text{Au(I)Ln}$ ,  $\text{Pd(0)}$ ) with an ammonium  $[\text{N-F}]^+$  type fluorination reagent which has a non-coordinating counter ion (Scheme 10). Such species (intermediate **1-A** in Scheme 10) is expected to be highly active, and its Lewis acidity is expected to be stronger than the corresponding metal prior to fluorination. This is due to the higher valence of the metal and the presence of a non-coordinating counter anion (e.g.  $\text{BF}_4^-$  in case of Selectfluor). Our premise is that this cationic gold-fluorine species would be able to catalyze not only the reactions that cationic metal normally catalyze (e.g. hydration or cyclization of alkynes), with similar or even higher efficiency, more importantly, it could mediate additional new transformations that regular cationic metal is less known for. This is illustrated in

Scheme 10. For example, a fluoro-gold intermediate **1-C** may undergo reductive elimination, fluorodemetalation or nucleophilic displacement to give a vinyl fluoride (right in Scheme 10); or transmetalation with an organometallic reagent  $R_3M$  to give **1-D** (e.g.  $M = B, Si, Sn$ , etc.).<sup>34</sup> The weak M-F bond<sup>35</sup> and the strong B-F, Si-F and Sn-F bonds would drive the transmetalation. After reductive elimination, the low valence metal complex is re-fluorinated to resume its catalytic cycle. This strategy should deliver a diversity of fluorinated and non-fluorinated building blocks or targets.



**Scheme 10. Fluorination-enabled cationic metal complex and its catalytic cycle.**

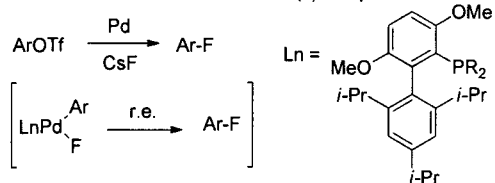
### 1.3.4 Literature reports involve Metal-F intermediate

Our proposed catalytic cycle has four key steps: 1) fluorination of low valence metal complex; 2) reductive elimination to give R-F compounds; 3) transmetalation of M-F to M-R; 4) fluorodemetalation. Metal catalysis involving those steps has emerged in the recent literature. Fluorination reagents (e.g. Selectfluor<sup>36,37</sup>) have become lately the oxidant of choice in transition metal-mediated C-H activation, fluorination, oxidation and coupling reactions, as

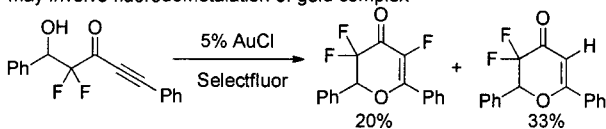
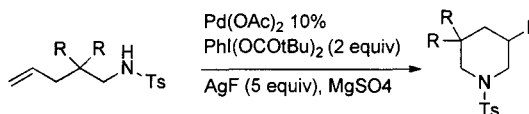
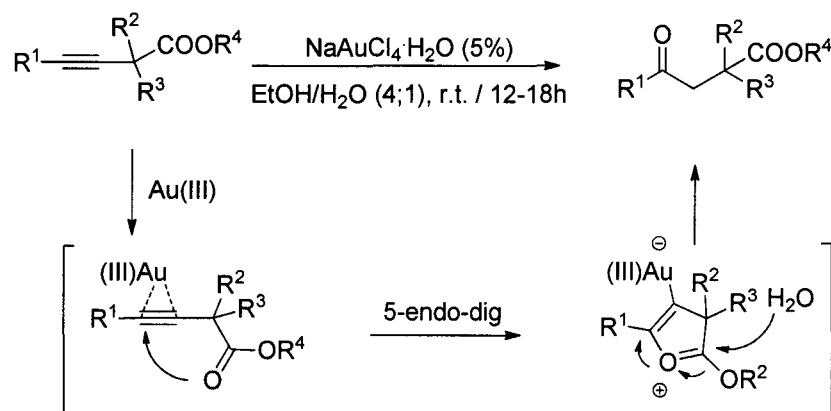
demonstrated by Ritter,<sup>38-40</sup> Sanford,<sup>29,41</sup> Gouverneur,<sup>42</sup> Zhang,<sup>34,43</sup> Michael,<sup>44</sup> among others. For the reductive elimination of R-M-F, Buchwald<sup>45</sup> (Scheme 11) and co-workers' recent breakthrough indicate that the correct choice of ligand is decisive for a successful outcome, allowing for the preparation of aryl fluoride from a stabilized 14-electron Pd(II) complex. The steric size of their ligand (*t*BuBrettPhos) may also compress the ArPdF angle, thereby forcing reductive elimination by bringing closer the aryl and fluorine substituents. For the fluorodemetalation process, Gouverneur and coworkers have proposed a mechanism for the gold-catalyzed cyclization of fluoro alkynyl ketone,<sup>42</sup> although in very low yields (Scheme 11). In the case of nucleophilic displacement, Liu's method can be used in the synthesis of aliphatic system (Scheme 11), but still large excess of AgF (5 equiv) be used. Although promising, most of those studies are limited to aromatic systems and in many cases, a stoichiometric amount of the transition metal must be used. Compared to an aromatic system, transition metal catalysis in aliphatic systems may suffer from  $\beta$ -H elimination and some other side-reactions. But we believe it possible to overcome this problem with a systematic exploration of metal fluorine interaction. And our preliminary results show promising future.

**Buchwald's work**

Ar-F reductive elimination from Pd(II) complex

**Gouverneur's work**

may involve fluorodemetalation of gold complex

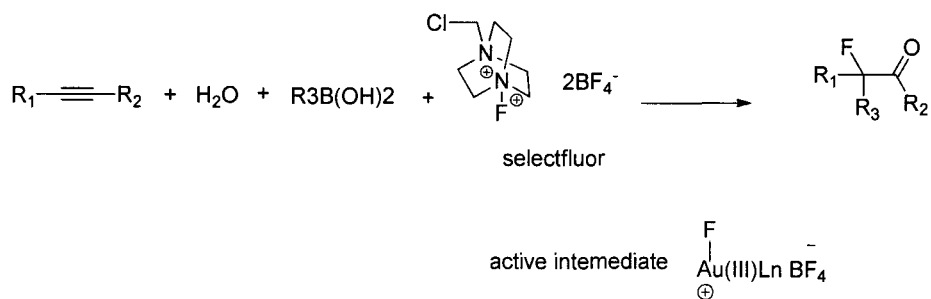
**Liu's work**may involve reductive elimination of  $\text{RPd(IV)F}$ **Scheme 11. Selected examples of literature reports involving Metal-F intermediate.****1.4 Outline of this thesis**

$\text{R}^1$ : Me,  $n\text{-C}_6\text{H}_{13}$ , Ph;  $\text{R}^2$  and  $\text{R}^3$ : alkenyl, alkyl, alkyl ether, alkyl ester;  $\text{R}^4$ : alkyl

Chapter 2 (*J.Org. Chem.* **2009**, 74, 1640)

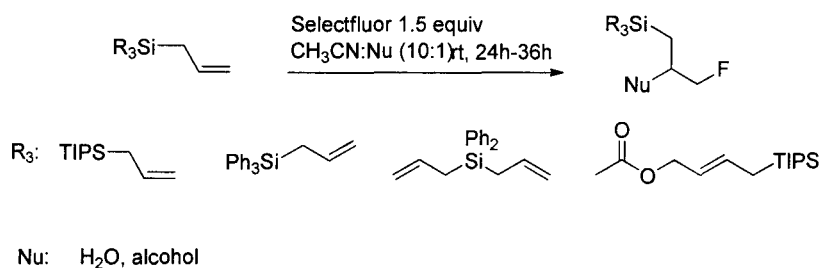
**Scheme 12. Synthesis of  $\gamma$ -keto esters through neighboring carbonyl group-assisted regioselective hydration of 3-alkynoates.**





**Chapter 3** (*Angew. chem., Int. Ed.* **2010**, 49,7247)

**Scheme 13. Fluorine-enabled cationic gold catalysis: functionalized hydration of alkynes.**



**Chapter 4** (*Synthesis*. **2011**, 15, 2383)

**Scheme 14. Synthesis of fluorohydrins through electrophilic fluorination of allyl silanes.**

## CHAPTER 2. GOLD CATALYZED HYDRATION OF ALKYNES

### 2.1 Introduction

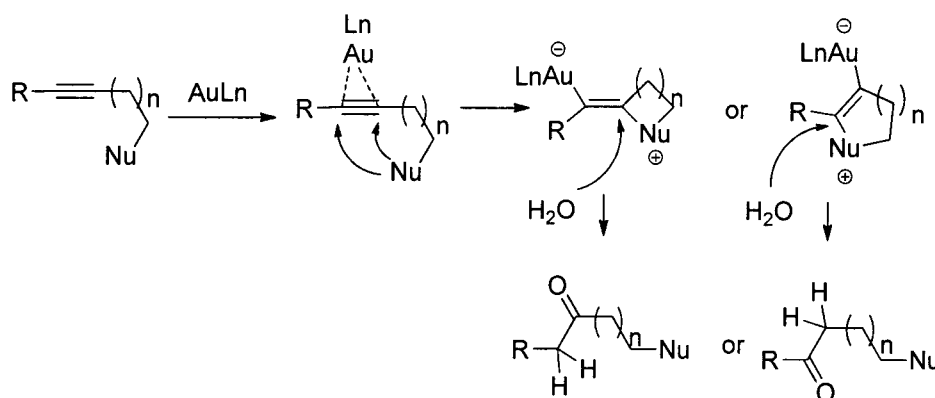
1,4-Dicarbonyl compounds are starting materials and intermediates in many important natural products and synthetic drug syntheses.<sup>46-48</sup> Unlike their 1,3 or 1,5-counterparts, the disconnection of 1,4-dicarbonyl compounds, especially of highly substituted 1,4-dicarbonyl compounds like  $\gamma$ -keto- $\alpha,\alpha$ -substituted esters, is not trivial. Radical or carbene<sup>49,50</sup> methodologies, or some other relatively complex methods<sup>51-53</sup> have to be used to synthesize them. A tactical approach that enables a one-step disconnection of highly substituted  $\gamma$ -keto esters could be the directed hydration of 3-alkynoates, provided this transformation can be carried out regioselectively, under mild conditions, and with good functional group tolerance. The attractiveness of this approach lies on the fact that the hydration of alkynes is one of the most straightforward methods to make carbonyl compounds. Unlike other syntheses of carbonyl compounds, the hydration of alkynes is an atom-economical addition of water without energy-intensive redox chemistry.<sup>54</sup> In addition, the alkyne functionality is chemically inert toward many reaction conditions, and so it can be considered as a masked ketone.

The mercury (II)-catalyzed hydration of alkynes has been known for more than a century. To avoid the use of toxic mercury(II) salts, various catalysts such as Brønsted acids<sup>55-57</sup> and metal catalysts, such as Ru(II)<sup>58-60</sup>, Ru(III)<sup>61</sup>, Rh(III)<sup>62</sup>, Ir<sup>63</sup>, Pt(II)<sup>64-67</sup>, Au<sup>68-71</sup> as well as other systems<sup>72-78</sup> have been examined. There are excellent catalysts for terminal alkynes but internal alkynes remain a challenge, in part because of regioselectivity issues. Gold catalysis is especially promising for the hydration of alkynes because of the higher affinity of gold towards alkynes compared to other common oxygen- or nitrogen-containing functional groups. In 1991, Fukuda and coworkers reported the use of an Au (III) salt in refluxing aqueous methanol for the hydration of terminal alkynes to methyl ketones (Markovnikov addition). But their hydration of internal alkynes was sluggish and non-regioselective. Many other gold catalysts have been also examined, but only terminal alkynes showed good regioselectivity (Markovnikov products), and most reactions needed elevated temperatures or strong acid co-catalysts.<sup>68-71</sup> We are pleased to report a neighboring carbonyl group-assisted hydration of internal alkynes in the presence of a gold (III) catalyst that yields a highly regioselective synthesis of  $\gamma$ -keto esters.

## **2.2 Directed gold-catalyzed hydration of alkynes through neighboring group assistance**

In general, the regioselective hydration of internal alkynes may only proceed in the presence of a directing functionality (like heteroatoms, aromatic rings) nearby.<sup>79-85</sup> We proposed that with internal alkynes possessing a nucleophilic site Nu nearby (Scheme 15), this nucleophile could attack a gold activated triple bond

to form two regioisomeric cyclic intermediates. Although both carbons in the triple bond are prone to nucleophilic attack, one cyclic intermediate may be favored over the other according to Baldwin's rules.<sup>86</sup> If Nu is a carboxylic ester, this neighboring group assistance may then lead to a highly regioselective synthesis of  $\gamma$ -keto esters through an alkyne hydration process.



**Scheme 15. Directed gold-catalyzed hydration of alkynes through neighboring group assistance.**

## 2.3 Results and discussion

To test this hypothesis, we first examined the effect of transition metal catalysts on the hydration of 3-alkynoate **2-1a** (Table 1). Our selection of metal catalysts was based on the known alkynophilicity of gold (I), gold (III), platinum (II), and silver (I).<sup>87</sup> A strong acid alone<sup>55-57</sup> had no effect on **2-1a** (Table 1, entry 1).

Treatment of **2-1a** with Au(I) or PtCl<sub>2</sub> catalysts gave traces of hydration product **2-2a** at room temperature (Table 1, entries 2 - 5). Conversely, the addition of a strong acid to AuCl, or Au(PPh<sub>3</sub>)Cl produced the desired ketone but in less than desirable yields, due to side-reactions induced by the prevailing acidic conditions (Table 1, entries 6 and 7). On the other hand, the use of Au(III) catalysts such as

AuBr<sub>3</sub>, AuCl<sub>3</sub> or NaAuCl<sub>4</sub>·2H<sub>2</sub>O offered hope (Table 1, entries 8 - 10). After these results, we decided to investigate the effects of solvents and additives/ligands on the hydration of **2-1a** employing Au(III) catalysts. Using AuBr<sub>3</sub> in various solvent combinations did not improve the yield of **2-2a** significantly (Table 2, entries 1-5). We then tested a combination of AuBr<sub>3</sub> with various additives or ligands, such as *n*Bu<sub>4</sub>NBr, P(OEt)<sub>3</sub> or pyridine, with disappointing results (Table 2, entries 6-9). A complex mixture was observed when a combination of AuCl<sub>3</sub> and AgOTf in MeOH/H<sub>2</sub>O was used, whereas AuCl<sub>3</sub> alone produced **2-2a** in only 33% yield (Table 2, entries 10 and 11).

**Table 1. Screening of metal catalysts for the hydration of 2-1a.**

entry	catalyst (5%)	solvent	time	yield <sup>a</sup>
1	10%TsOH	CH <sub>2</sub> Cl <sub>2</sub> (S) <sup>b</sup>	24h	no RXN
2	PtCl <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub> (S)	12h	trace
3	Au(PPh <sub>3</sub> )Cl	CH <sub>2</sub> Cl <sub>2</sub> (S)	12h	trace
4	AuCl	CH <sub>2</sub> Cl <sub>2</sub> (S)	12h	trace
5		CH <sub>2</sub> Cl <sub>2</sub> (S)	12h	trace
6	AuCl, 10%TsOH	CH <sub>2</sub> Cl <sub>2</sub> (S)	24h	50%
7	Au(PPh <sub>3</sub> )Cl, 10% H <sub>2</sub> SO <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub> (S)	12h	60%
8	AuBr <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub> (S)	12h	70%
9	AuCl <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub> (S)	12h	41%
10	NaAuCl <sub>4</sub> ·2H <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub> (S)	12h	71%

<sup>a</sup> Yields are based on <sup>1</sup>H NMR. <sup>b</sup> CH<sub>2</sub>Cl<sub>2</sub> saturated with water.

After screening  $\text{NaAuCl}_4 \cdot 2\text{H}_2\text{O}$  using different solvent combinations (Table 2, entries 12-17), we concluded that  $\text{NaAuCl}_4 \cdot 2\text{H}_2\text{O}$  in  $\text{EtOH}/\text{H}_2\text{O}(4:1)$  offered the best conditions for the hydration of alkyne **2-1a**. When methanol was used as solvent, the reaction gave a mixture of **2-2a** and the corresponding methyl ester due to transesterification (Table 2, entry 17). When a smaller catalyst loading ( $\text{NaAuCl}_4 \cdot 2\text{H}_2\text{O}$ , 2%) was used, the reaction was slower, but hydration of compound **2-2a** still could be completed in 24h. Using these optimal conditions in hand, we explored the scope of this reaction (Table 3). The hydration proceeded smoothly in high yields with regioselectivity, and was tolerant of an ether, double bond, or other ester functionalities (Table 3, entries 4, 5, and 8, respectively). Indeed, only one regioisomer was detected among all the crude products examined. The steric hindrance of the quaternary  $\alpha$ -carbon could be ruled out as the reason for the high selectivity of the hydration because a 3-alkynoate possessing no substituents in its  $\alpha$ -carbon also showed excellent regioselectivity after hydration (Table 3, entry 10). The stereoelectronic effects of a phenyl group could account for the lower yield observed in (Table 3, entry 7). The hydration of 2-fluoro-3-alkynoate **2-1k** gives  $\alpha,\beta$ -unsaturated ester **2-2k** (Table 3 entry 11) through concomitant elimination of HF during the hydration process.

**Table 2. Screening of solvents and additives.**

$n\text{-C}_6\text{H}_{13}\text{-C}\equiv\text{C-C(COOEt)(CH}_3)_2$  (2-1a)  $\xrightarrow[\text{r.t.}]{\text{Catalyst}}$   $n\text{-C}_6\text{H}_{13}\text{-C(=O)-CH}_2\text{-C(COOEt)(CH}_3)_2$  (2-2a)

entry	catalyst (5%)/additives	solvent	time	yield <sup>a</sup>
1	AuBr <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub> (S) <sup>b</sup>	12h	70%
2	AuBr <sub>3</sub>	MeOH/ H <sub>2</sub> O (10:1)	12h	17%
3	AuBr <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub> /H <sub>2</sub> O (100:1)	72h	trace
4	AuBr <sub>3</sub>	<i>t</i> -BuOH/H <sub>2</sub> O (10:1)	12h	25%
5	AuBr <sub>3</sub>	CH <sub>3</sub> CN/H <sub>2</sub> O(10:1)	12h	35%
6	AuBr <sub>3</sub> /Bu <sub>4</sub> NBr(5%)	CH <sub>2</sub> Cl <sub>2</sub> (S)	12h	6%
7	AuBr <sub>3</sub> /Bu <sub>4</sub> NBr(5%)	MeOH/H <sub>2</sub> O(10:1)	12h	trace
8	AuBr <sub>3</sub> /pyridine (5%)	MeOH/H <sub>2</sub> O (10:1)	12h	No RXN
9	AuBr <sub>3</sub> /P(OEt) <sub>3</sub> (5%)	MeOH/H <sub>2</sub> O (10:1)	12h	No RXN
10	AuCl <sub>3</sub>	MeOH/H <sub>2</sub> O(10:1)	24h	33%
11	AuCl <sub>3</sub> /AgOTf (15%)	MeOH/H <sub>2</sub> O(10:1)	24h	complex
12	NaAuCl <sub>4</sub> ·2H <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub> (S)	12h	71%
13	NaAuCl <sub>4</sub> ·2H <sub>2</sub> O	<i>t</i> -BuOH/H <sub>2</sub> O	12h	56%
14	NaAuCl <sub>4</sub> ·2H <sub>2</sub> O	EtOH/H <sub>2</sub> O(50:1)	12h	33%
15	NaAuCl <sub>4</sub> ·2H <sub>2</sub> O	EtOH/H <sub>2</sub> O(4:1)	12h	78%
16	NaAuCl <sub>4</sub> ·2H <sub>2</sub> O	EtOH/H <sub>2</sub> O(1:1)	12h	33%
17	NaAuCl <sub>4</sub> ·2H <sub>2</sub> O	MeOH/H <sub>2</sub> O(10:1)	12h	mixture <sup>c</sup>

<sup>a</sup> Yields are based on <sup>1</sup>H NMR. <sup>b</sup> CH<sub>2</sub>Cl<sub>2</sub> saturated by water. <sup>c</sup> Mixture of **2-2a** and corresponding methyl ester.

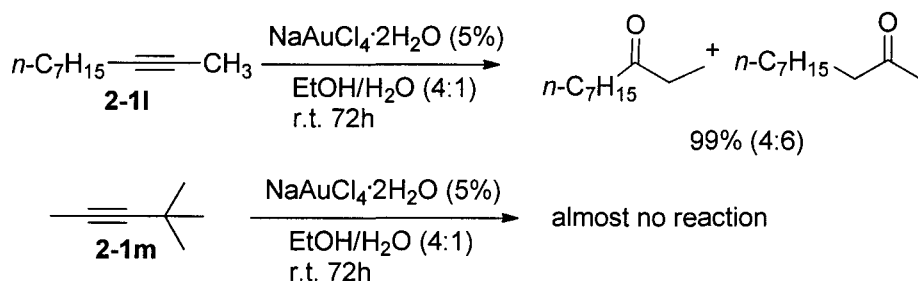
**Table 3. Au(III)-catalyzed hydration of internal 3-alkynoates.**

$  \begin{array}{c}  \text{R}^1-\text{C}\equiv\text{C}-\text{C}(\text{R}^2)(\text{R}^3)\text{COOR}^4 \\  \text{2-1}  \end{array}  \xrightarrow[\text{EtOH/H}_2\text{O (4:1), r.t. / 12-18h}]{\text{NaAuCl}_4\cdot\text{H}_2\text{O (5\%)}}  \begin{array}{c}  \text{R}^1-\text{C}(=\text{O})-\text{CH}(\text{R}^2)-\text{C}(\text{R}^3)\text{COOR}^4 \\  \text{2-2}  \end{array}  $			
entry	2-1	2-2	yield %
1	$  \begin{array}{c}  n\text{-C}_6\text{H}_{13}-\text{C}\equiv\text{C}-\text{C}(\text{CH}_3)_2\text{COOEt} \\  \text{2-1a}  \end{array}  $	$  \begin{array}{c}  n\text{-C}_6\text{H}_{13}-\text{C}(=\text{O})-\text{CH}(\text{CH}_3)-\text{C}(\text{CH}_3)_2\text{COOEt} \\  \text{2-2a}  \end{array}  $	78%
2	$  \begin{array}{c}  n\text{-C}_6\text{H}_{13}-\text{C}\equiv\text{C}-\text{C}(\text{CH}_3)(\text{C}_8\text{H}_{17})\text{COOEt} \\  \text{2-1b}  \end{array}  $	$  \begin{array}{c}  n\text{-C}_6\text{H}_{13}-\text{C}(=\text{O})-\text{CH}(\text{CH}_3)-\text{C}(\text{C}_8\text{H}_{17})\text{COOEt} \\  \text{2-2b}  \end{array}  $	93%
3	$  \begin{array}{c}  n\text{-C}_6\text{H}_{13}-\text{C}\equiv\text{C}-\text{C}(\text{CH}_3)(\text{CH}_2\text{CH}_2\text{CH}_3)\text{COOEt} \\  \text{2-1c}  \end{array}  $	$  \begin{array}{c}  n\text{-C}_6\text{H}_{13}-\text{C}(=\text{O})-\text{CH}(\text{CH}_3)-\text{C}(\text{CH}_2\text{CH}_2\text{CH}_3)\text{COOEt} \\  \text{2-2c}  \end{array}  $	74%
4	$  \begin{array}{c}  n\text{-C}_6\text{H}_{13}-\text{C}\equiv\text{C}-\text{C}(\text{CH}_3)(\text{CH}_2\text{CH}_2\text{OMe})\text{COOEt} \\  \text{2-1d}  \end{array}  $	$  \begin{array}{c}  n\text{-C}_6\text{H}_{13}-\text{C}(=\text{O})-\text{CH}(\text{CH}_3)-\text{C}(\text{CH}_2\text{CH}_2\text{OMe})\text{COOEt} \\  \text{2-2d}  \end{array}  $	89%
5	$  \begin{array}{c}  n\text{-C}_6\text{H}_{13}-\text{C}\equiv\text{C}-\text{C}(\text{CH}_3)(\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2)\text{COOEt} \\  \text{2-1e}  \end{array}  $	$  \begin{array}{c}  n\text{-C}_6\text{H}_{13}-\text{C}(=\text{O})-\text{CH}(\text{CH}_3)-\text{C}(\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2)\text{COOEt} \\  \text{2-2e}  \end{array}  $	91%
6	$  \begin{array}{c}  n\text{-C}_6\text{H}_{13}-\text{C}\equiv\text{C}-\text{C}(\text{CH}_3)(\text{CH}_2\text{CH}=\text{CH}_2)\text{COOEt} \\  \text{2-1f}  \end{array}  $	$  \begin{array}{c}  n\text{-C}_6\text{H}_{13}-\text{C}(=\text{O})-\text{CH}(\text{CH}_3)-\text{C}(\text{CH}_2\text{CH}=\text{CH}_2)\text{COOEt} \\  \text{2-2f}  \end{array}  $	91%
7	$  \begin{array}{c}  \text{Ph}-\text{C}\equiv\text{C}-\text{C}(\text{CH}_3)(\text{CH}_2\text{CH}=\text{CH}_2)\text{COOEt} \\  \text{2-1g}  \end{array}  $	$  \begin{array}{c}  \text{Ph}-\text{C}(=\text{O})-\text{CH}(\text{CH}_3)-\text{C}(\text{CH}_2\text{CH}=\text{CH}_2)\text{COOEt} \\  \text{2-2g}  \end{array}  $	58%
8	$  \begin{array}{c}  \text{C}_6\text{H}_{13}-\text{C}\equiv\text{C}-\text{C}(\text{CH}_3)(\text{CH}_2\text{CH}_2\text{C}(\text{OCH}_3)=\text{O})\text{CO}_2\text{Et} \\  \text{2-1h}  \end{array}  $	$  \begin{array}{c}  n\text{-C}_6\text{H}_{13}-\text{C}(=\text{O})-\text{CH}(\text{CH}_3)-\text{C}(\text{CH}_2\text{CH}_2\text{C}(\text{OCH}_3)=\text{O})\text{CO}_2\text{Et} \\  \text{2-2h}  \end{array}  $	92%
9	$  \begin{array}{c}  \text{CH}_3\text{C}\equiv\text{C}-\text{C}(\text{CH}_3)(\text{CH}_2\text{CH}_2\text{COOMe})\text{COOEt} \\  \text{2-1i}  \end{array}  $	$  \begin{array}{c}  \text{CH}_3\text{C}(=\text{O})-\text{CH}(\text{CH}_3)-\text{C}(\text{CH}_2\text{CH}_2\text{COOMe})\text{COOEt} \\  \text{2-2i}  \end{array}  $	80%
10	$  \begin{array}{c}  \text{C}_6\text{H}_{13}-\text{C}\equiv\text{C}-\text{CH}_2\text{C}(=\text{O})\text{OEt} \\  \text{2-1j}  \end{array}  $	$  \begin{array}{c}  \text{C}_6\text{H}_{13}-\text{C}(=\text{O})-\text{CH}_2\text{C}(=\text{O})\text{OEt} \\  \text{2-2j}  \end{array}  $	74%
11	$  \begin{array}{c}  \text{C}_6\text{H}_{13}-\text{C}\equiv\text{C}-\text{CH}(\text{F})\text{C}(=\text{O})\text{OEt} \\  \text{2-1k}  \end{array}  $	$  \begin{array}{c}  \text{C}_6\text{H}_{13}-\text{C}(=\text{O})-\text{CH}=\text{CH}\text{C}(=\text{O})\text{OEt} \\  \text{2-2k}  \end{array}  $	74%

Reactions were performed using 5 mol% NaAuCl<sub>4</sub>·2H<sub>2</sub>O, alkyne 2-1 (0.5 mmol), EtOH/H<sub>2</sub>O (4:1, 1.0 mL).

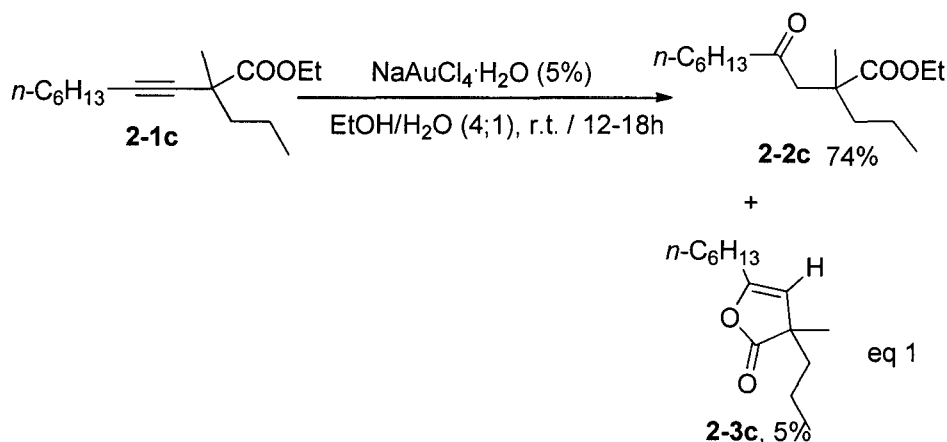


The adjacent carbonyl group in alkyne **2-1** plays an important role in both, reaction rate and regioselectivity. For example, the hydration of dec-2-yne **2-1l** under similar conditions was much slower (Scheme 16, top), and although the chemical yield was high, the regioselectivity was poor. The hydration of the sterically demanding 4,4-dimethylpent-2-yne **2-1m** was even slower; indeed, after 72 h, almost no reaction had taken place (Scheme 16, bottom). These results were in sharp contrast with the hydration of  $\beta$ -alkynyl esters. Even the hydration of sterically encumbered  $\beta$ -alkynyl esters **2-1h** proceeded smoothly at room temperature (Table 3, entries 8 ).



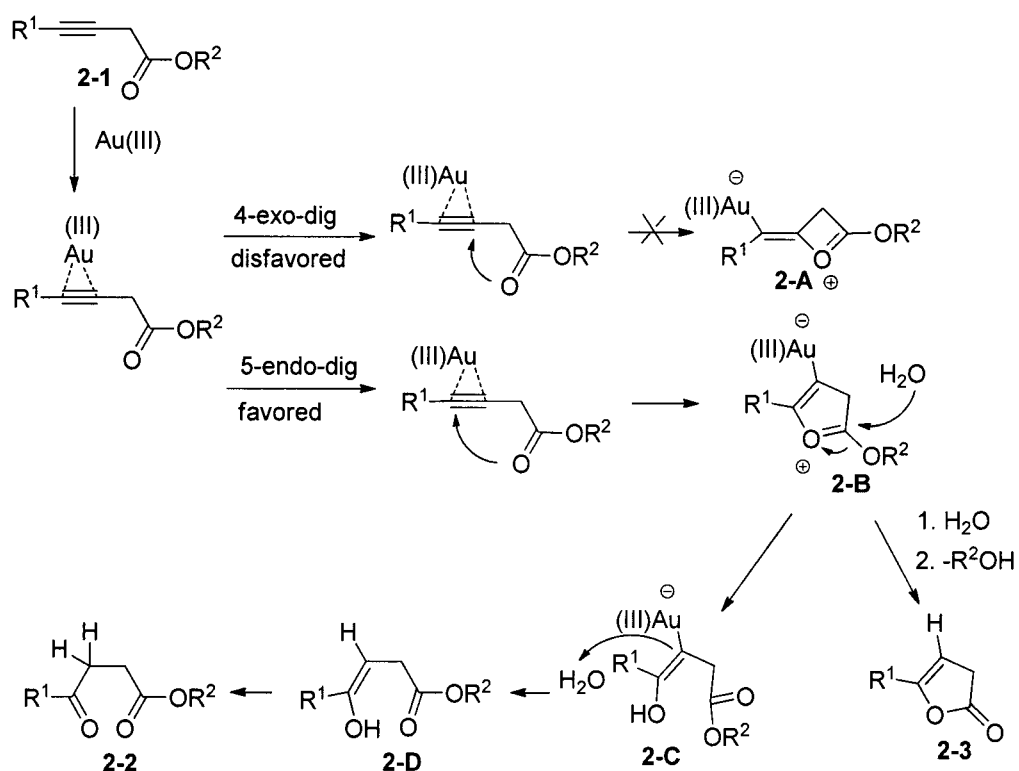
**Scheme 16. Hydration of simple internal alkynes.**

It is noteworthy that in some cases we obtained small or trace amounts of a cyclic by-product (e.g., **2-3c** in eq 1).

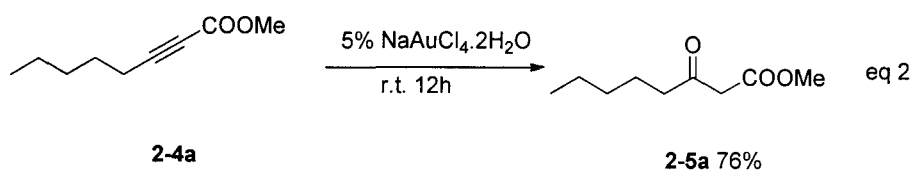


The proposed mechanism for the reaction, based on similar reaction systems,<sup>88</sup> is shown in Scheme 17. First, the gold (III) catalyst coordinates with alkyne **2-1**, activating the triple bond, and triggering the carbonyl group nearby which acts as a nucleophile to attack the triple bond to form a cyclized vinyl gold intermediate of type **2-A** or **2-B**.<sup>89,90</sup> According to Baldwin's rules<sup>86</sup>, if the carbonyl oxygen attacks the  $\beta$ -carbon, it is considered a *4-exo-dig* process, which is disfavored. But if the carbonyl oxygen attacks the  $\gamma$ -carbon, it would then be a *5-endo-dig* attack, which is regarded as favored.<sup>91,92</sup> For example; Hashmi and co-workers have reported the cyclization of an ethynylketone to a furan through *5-endo-dig* process.<sup>61</sup> Thus, **2-B** should be the predominating intermediate. Then, upon water attack to **2-B**, this forms the ring-opened product **2-C**, which in turn would form intermediate **2-D** by proto-deauration. Finally, isomerization of **2-D** produced  $\gamma$ -keto ester **2-2**. A competing side reaction, namely the elimination of  $R^2OH$  from **2-B**, is also possible. This would account for the trace amounts of cyclic byproduct obtained in some cases (eq. 1).

Hydration of 2-alkynoate **2-4a** under similar condition gave the  $\beta$ -keto ester **2-5a** in high yield (eq 2); this reaction is also highly regioselective. Its selectivity may arise through the electronic effect of the ester group. Due to the strong electron withdrawing effect of the conjugated ester, the  $\beta$ -carbon of **2-4a** is more electronically deficient, promoting an attack by water to this position to give **2-5a**.



**Scheme 17. Proposed mechanism for the hydration of 3-alkynoates.**



## 2.4 Summary and future direction

In summary, we have developed an effective and straightforward hydration of 3-alkynoates in the presence of catalytic amounts of Au (III) salt in aqueous ethanol at room temperature to give  $\gamma$ -keto esters regioselectively and in high yields. This mild and atom-economical method can be used effectively with a wide range of substrates, yielding densely functionalized products. With a propargyl ester this

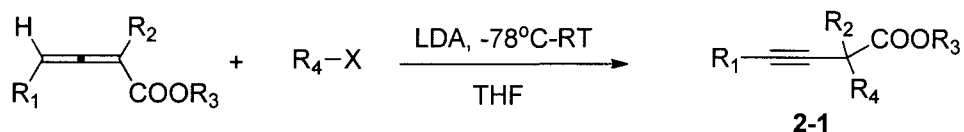
reaction yields  $\beta$ -keto esters in high yield. The broader applications of this reaction in organic synthesis are currently under investigation.

## 2.5 Experimental

### General

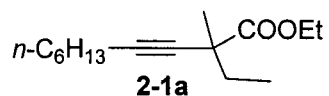
$^1\text{H}$ ,  $^{13}\text{C}$  NMR spectra were recorded at 500, 126 MHz respectively, using  $\text{CDCl}_3$  as a solvent. The chemical shifts are reported in  $\delta$  (ppm) values relative to  $\text{CHCl}_3$  ( $\delta$  7.26 ppm for  $^1\text{H}$  NMR and  $\delta$  77.0 ppm for  $^{13}\text{C}$  NMR), multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), m (multiplet) and br (broad). Coupling constants,  $J$ , are reported in Hertz. Coupling constants are reported in hertz (Hz). All air and/or moisture sensitive reactions were carried out under argon atmosphere. Solvents (tetrahydrofuran, ether, dichloromethane and DMF) were chemically dried using a commercial solvent purification system. All other reagents and solvents were employed without further purification. The products were purified using a Biotage flash+ system or Chromatotron apparatus or a regular glass column. TLC was developed on Merck silica gel 60 F254 aluminum sheets. Elemental analysis was performed at Atlantic Microlabs Inc., Norcross, Georgia 30091. Accurate mass determinations were performed at the Nebraska Center for Mass Spectrometry, University of Nebraska-Lincoln, Nebraska 68588.

### General procedure for preparation of 3-alkynoates **2-1**<sup>93,94</sup>



To an oven-dried, air-free 10 mL flask of an allenolate (0.5mmol) was added dry THF (2 mL) and the reaction mixture was cooled down to  $-78^\circ\text{C}$ ; LDA (2M in THF, 0.375 mL, 0.75mmol) was then added slowly over 5 min. The reaction mixture was stirred at  $-78^\circ\text{C}$  for 5 min, and then alkyl bromide (0.75 mmol) was injected dropwise slowly. The resulting solution was stirred for 10 min, then warmed up to room temperature, and stirred overnight at room temperature. The reaction mixture was then quenched with saturated  $\text{NH}_4\text{Cl}$  solution (2-3 mL). After stirring for 5 mins at the room temperature, the resulting aqueous mixture was extracted with ether (three times) and the combined organic layers were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was purified by flash silica gel chromatography (25%  $\text{CH}_2\text{Cl}_2$  in hexane - 50%  $\text{CH}_2\text{Cl}_2$  in hexane) to give the product  $\alpha,\alpha$ -disubstituted  $\beta$ -alkynyl esters.

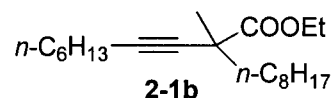
### Spectroscopic data of compounds **2-1**.



Compound **2-1a**: ethyl 2-ethyl-2-methyldec-3-ynoate

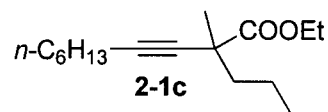
Colorless oil, 74%:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.88 (t,  $J$  = 6.5 Hz, 3H), 0.95 (t,  $J$  = 7 Hz, 3H), 1.25-1.32 (m, 3H), 1.35-1.41 (m, 2H), 1.39 (s, 2H), 1.46-1.51 (m,

2H), 1.61-1.66 (m, 2H), 1.79-1.84 (m, H), 2.18 (t,  $J = 7$  Hz, 2H), 4.16 (q,  $J = 7$  Hz, 2H).



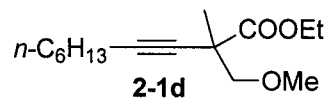
Compound **2-1b**: ethyl 2-methyl-2-octyldec-3-ynoate

Colorless oil, 67%:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.85-0.89 (m, 6H), 1.24-1.33 (m, 17H), 1.39 (s, 3H), 1.35-1.45 (m, 2H), 1.45-1.51 (m, 2H), 1.55-1.61 (m, 2H), 1.73-1.77 (m, 2H), 2.18 (t,  $J = 7$  Hz, 2H), 4.16 (q,  $J = 7$  Hz, 2H).



Compound **2-1c**: ethyl 2-methyl-2-propyldec-3-ynoate

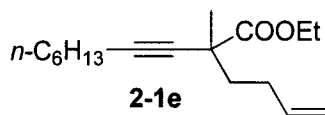
Colorless oil, 54%:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.87-0.92 (m, 6H), 1.25-1.31 (m, 7H), 1.31-1.38 (m, 4H), 1.40 (s, 3H), 1.44-1.50 (m, 2H), 1.54-1.60 (m, 1H), 1.73-1.79 (m, 1H), 2.18 (t,  $J = 6.5$  Hz, 2H), 4.16 (q,  $J = 7.0$  Hz, 2H).



Compound **2-1d**: ethyl 2-(methoxymethyl)-2-methyldec-3-ynoate

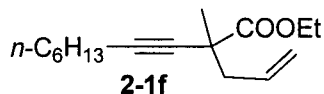
Colorless oil, 90%:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.85 (t,  $J = 7.0$  Hz, 3H), 1.23-1.29 (m, 7H), 1.31-1.36 (m, 2H), 1.39 (s, 3H), 1.42-1.46 (m, 2H), 2.14 (t,  $J = 7.0$

Hz, 2H), 3.33 (s, 3H), 3.45 (d,  $J = 8.5$  Hz, 1H), 3.59 (d,  $J = 9.0$  Hz, 1H), 4.16 (q,  $J = 7.0$  Hz, 2H).



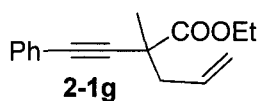
Compound **2-1e**: ethyl 2-(but-3-en-1-yl)-2-methyldec-3-ynoate

Colorless oil, 81%:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.88 (t,  $J = 6.5$  Hz, 3H), 1.25-1.32 (m, 7H), 1.36-1.40 (m, 2H), 1.42 (s, 3H), 1.46-1.50 (m, 2H), 1.65-1.70 (m, 1H), 1.86-1.92 (m, 1H), 2.11-2.14 (m, 2H), 2.18 (d,  $J = 6.5$  Hz, 2H), 4.16 (q,  $J = 6.5$  Hz, 2H), 4.93-5.03 (m, 2H), 5.77-5.83 (m, 1H).



Compound **2-1f**: ethyl 2-allyl-2-methyldec-3-ynoate

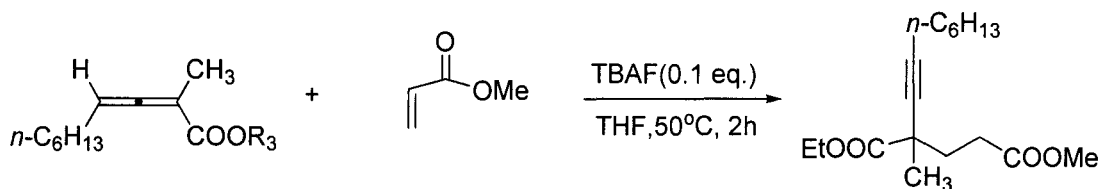
Colorless oil, 88%:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.89 (t,  $J = 7.0$  Hz, 3H), 1.26-1.31 (m, 7H), 1.4 (s, 3H), 1.38-1.52 (m, 4H), 2.19 (t,  $J = 6.5$  Hz, 2H), 2.38-2.42 (m, 1H), 2.52-2.56 (m, 1H), 4.17 (q,  $J = 7$  Hz, 2H), 5.08-5.11 (m, 2H), 5.82-5.88 (m, 1H).



Compound **2-1g**: ethyl 2-methyl-2-(phenylethynyl)pent-4-enoate

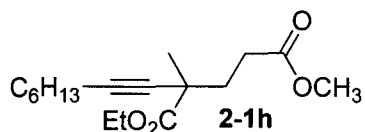
Colorless oil, 79%:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.32 (t,  $J = 7.0$  Hz, 3H), 1.55 (s, 3H), 2.53-2.57 (m, H), 2.67-2.71 (m, H), 4.24 (q,  $J = 7.0$  Hz, 2H), 5.16-5.20 (m, 2H), 5.92-5.98 (m, 1H), 7.20-7.30 (m, 3H), 7.44-7.45 (m, 2H).

**General procedure for preparation of 2-1i and 2-1h**<sup>94</sup>



To a solution of ethyl  $\alpha$ -methyl- $\gamma$ -(*n*-hexyl)-allenoate (63 mg, 0.3 mmol) and methyl acrylate (31 mg, 0.36 mmol) in THF (2.0 mL) was added a solution of TBAF in THF (1.0 M solution in THF, 0.03 mL). The mixture was stirred for 2 hr at 50 °C; afterwards the solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (eluent: ethyl acetate/petroleum ether, 1:20) to give product **1h** (71 mg, 80%) as a colorless oil.

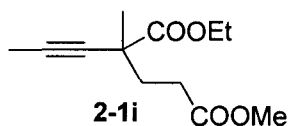
**Spectroscopic data of compounds 2-1i and 2-1h**



Compound **2-1h**: 1-ethyl 5-methyl 2-methyl-2-(oct-1-yn-1-yl)pentanedioate



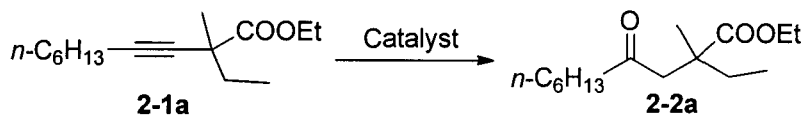
a colorless oil; IR (neat):  $\nu$  2933, 2859, 1739, 1437, 1238, 1024  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  0.87 (3H, t,  $J$  = 7.0 Hz), 1.26-1.50 (14H, m), 1.87-1.92 (1H, m), 1.93-2.18 (m, 3H), 2.39-2.45 (m, 1H), 2.49-2.55 (m, 1H), 3.66 (s, 3H), 4.16 (q,  $J$  = 7.0 Hz, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz)  $\delta$  14.0, 14.1, 18.7, 22.5, 26.0, 28.4, 28.7, 30.5, 31.3, 34.8, 42.2, 51.6, 61.4, 80.0, 84.1, 173.4, 173.6; MS (EI)  $m/z$  286 ( $\text{M}^+$ , 100), 252, 214; Anal. Calcd. for  $\text{C}_{17}\text{H}_{28}\text{O}_4$ : C, 68.89; H, 9.52. Found: C, 68.94; H, 9.61.



Compound **2-1i**: 1-ethyl 5-methyl 2-methyl-2-(prop-1-yn-1-yl)pentanedioate

a colorless oil; IR (neat):  $\nu$  2983, 1738, 1443, 1241, 1115, 1022, 1126  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  1.24 (t,  $J$  = 7.0 Hz, 3H), 1.39 (s, 3H), 1.78 (s, 3H), 1.85-1.91 (m, 1H), 2.09-2.15 (m, 1H), 2.35-2.42 (m, 1H), 2.45-2.52 (m, 1H), 3.63 (s, 3H), 4.14 (q,  $J$  = 7.0 Hz, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz)  $\delta$  3.5, 14.0, 25.9, 30.4, 34.8, 42.2, 51.5, 61.4, 79.0, 79.4, 173.2, 173.5; MS (EI)  $m/z$  226 ( $\text{M}^+$ , 100), 178, 151; Anal. Calcd. for  $\text{C}_{12}\text{H}_{18}\text{O}_4$ : C, 63.70; H, 8.02. Found: C, 63.90; H, 8.13.

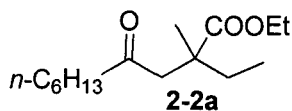
### General procedure for hydration of alkyne **2-1**.



$\text{NaAuCl}_4 \cdot 2\text{H}_2\text{O}$  (3mg, 5%) was added to a stirred solution of alkyne **2-1a** (71.4 mg, 0.3 mmol) in  $\text{EtOH}/\text{H}_2\text{O}$  (4:1, 1 mL). After stirring for 12-18 h at r.t., the

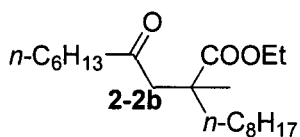
reaction mixture was concentrated under reduced pressure and the crude product was purified by flash silica gel chromatography (EtOAc/hexane 1: 20 - 1:4) to give the final product **2-2a** as a colorless oil (**60** mg, 78%).

#### Spectroscopic data of compounds 2-2.



Compound **2-2a**: ethyl 2-ethyl-2-methyl-4-oxodecanoate

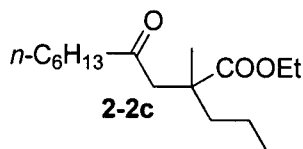
Colorless oil, 78%: IR (neat):  $\nu$  2957, 2930, 2859, 1734, 1457, 1177, 1134  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.83-0.89 (m, 6H), 1.20(s, 3H), 1.22-1.32 (m, 9H), 1.52-1.67 (m, 4H), 2.34-2.38 (m, 2H), 2.49 (d,  $J$  = 17.5 Hz, 1H), 2.89 (d,  $J$  = 17.5 Hz, 1H), 4.13 (q,  $J$  = 7.0 Hz, 2H);  $^{13}\text{C}$ -NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.7, 14.2, 14.4, 21.3, 22.7, 24.0, 29.1, 31.8, 32.7, 43.6, 44.0, 50.8, 60.6, 176.8, 209.1; GC/MS (EI)  $m/z$ : 257, 211, 171, 143, 113, 85, 69, 42; HRMS (ESI) calcd. for ( $\text{C}_{15}\text{H}_{28}\text{O}_3 + \text{Na}$ ) $^+$  279.1936, found 279.1930.



Compound **2-2b**: ethyl 2-methyl-2-octyl-4-oxodecanoate

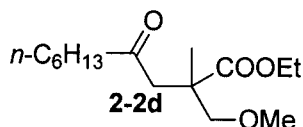
Colorless oil, 93%: IR (neat):  $\nu$  2927, 2855, 2359, 1717, 1457, 1176  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.87 (t,  $J$  = 7.0 Hz, 6H), 1.20-1.29 (m, 24H), 1.52-1.55 (m, 4H), 2.29-2.36 (m, 2H), 2.49 (d,  $J$  = 17.5 Hz, 1H), 2.88 (d,  $J$  = 17.5 Hz, 1H),

4.12 (q,  $J = 7.0$  Hz, 2H);  $^{13}\text{C}$ -NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.2, 14.3, 14.4, 21.8, 22.7, 22.9, 24.0, 24.3, 29.1, 29.4, 29.6, 30.2, 31.8, 32.1, 40.1, 43.6, 43.7, 51.1, 60.6, 176.9, 209.1; GC/MS (EI)  $m/z$ : 341, 295, 270, 227, 181, 163, 135, 112. HRMS (ESI) calcd. for  $(\text{C}_{21}\text{H}_{40}\text{O}_3 + \text{Na})^+$  363.2875, found 363.2872.



Compound **2-2c**: ethyl 2-methyl-4-oxo-2-propyldecanoate

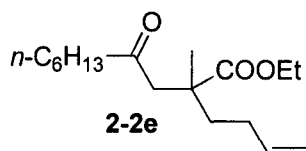
Colorless oil, 74%: IR (neat):  $\nu$  2931, 2873, 1717, 1457, 1176  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.86-0.90 (m, 6H), 1.19-1.31 (m, 14H), 1.46-1.55 (m, 4H), 2.32-2.36 (m, 2H), 2.50 (d,  $J = 17.5$  Hz, 1H), 2.89 (d,  $J = 17.5$  Hz, 1H), 4.12 (q,  $J = 7.5$  Hz, 2H);  $^{13}\text{C}$ -NMR(125MHz,  $\text{CDCl}_3$ ):  $\delta$  14.2, 14.4, 14.7, 17.6, 21.8, 22.7, 24.0, 29.1, 31.8, 42.4, 43.6, 43.8, 51.1, 60.6, 176.9, 209.1; GC/MS (EI)  $m/z$ : 271, 225, 197, 157, 112, 85, 42.



Compound **2-2d**: ethyl 2-(methoxymethyl)-2-methyl-4-oxodecanoate

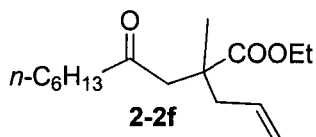
Colorless oil, 89%: IR (neat):  $\nu$  2927, 2857, 2359, 1733, 1457, 1110  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.85-0.88 (m, 3H), 1.21-1.29 (m, 12H), 1.52-1.55 (m, 2H), 2.36 (t,  $J = 6.5$  Hz, 2H), 2.63 (d,  $J = 17.5$  Hz, 1H), 2.90 (d,  $J = 17.5$  Hz, 1H),

3.30 (s, 3H), 3.39 (d,  $J = 9.0$  Hz, 1H), 3.53 (d,  $J = 9.0$  Hz, 1H), 4.13 (q,  $J = 7.5$  Hz, 2H);  $^{13}\text{C}$ -NMR(125MHz,  $\text{CDCl}_3$ ):  $\delta$  14.2, 14.3, 21.3, 22.7, 24.0, 29.1, 29.9, 31.8, 43.5, 45.1, 47.0, 59.4, 60.8, 175.5, 209.3; GC/MS (EI)  $m/z$ : 273, 227, 187, 145, 99, 42.



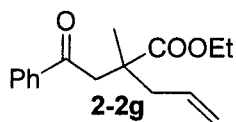
Compound **2-2e**: ethyl 2-(but-3-en-1-yl)-2-methyl-4-oxodecanoate

Colorless oil, 91%: IR (neat):  $\nu$  2929, 2857, 1717, 1457, 1176,  $910\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.86 (t,  $J = 7.0$  Hz, 3H), 1.21-1.30 (m, 12H), 1.52-1.66 (m, 4H), 1.94-2.00 (m, 2H), 2.32-2.36 (m, 2H), 2.52 (d,  $J = 17.5$  Hz, 1H), 2.89 (d,  $J = 17.5$  Hz, 1H), 4.11 (q,  $J = 7.5$  Hz, 2H), 5.72-5.77 (m, 1H), 4.93 (d,  $J = 10.0$  Hz, 1H), 4.99 (d,  $J = 10.0$  Hz, 1H);  $^{13}\text{C}$ -NMR (125MHz,  $\text{CDCl}_3$ ):  $\delta$  14.2, 14.3, 21.8, 22.7, 24.0, 28.7, 29.1, 31.8, 39.1, 43.5, 51.0, 60.7, 114.9, 138.3, 176.6, 208.9; GC/MS (EI)  $m/z$ : 283, 237, 209, 182, 151, 95, 42. HRMS (ESI) calcd. for  $(\text{C}_{17}\text{H}_{30}\text{O}_3 + \text{Na})^+$  305.2093, found 305.2084.



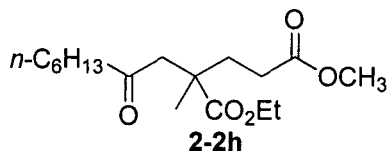
Compound **2-2f**: ethyl 2-allyl-2-methyl-4-oxodecanoate

Colorless oil, 91%: IR (neat):  $\nu$  2929, 2857, 2359, 1717, 1457, 1175, 917  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.86 (t,  $J$  = 7.0 Hz, 3H), 1.20-1.29 (m, 12H), 1.50-1.53 (m, 2H), 2.31-2.34 (m, 4H), 2.53 (d,  $J$  = 17.5 Hz, 1H), 2.81 (d,  $J$  = 17.5 Hz, 1H), 4.09-4.13 (m, 2H), 5.00-5.06 (m, 2H), 5.66-5.71 (m, 1H);  $^{13}\text{C}$ -NMR (125MHz,  $\text{CDCl}_3$ ):  $\delta$  14.2, 14.3, 22.3, 22.7, 23.9, 29.0, 31.8, 43.3, 43.5, 43.6, 50.1, 60.7, 118.7, 133.6, 176.5, 208.9; GC/MS (EI)  $m/z$ : 269, 223, 195, 141, 113, 42. HRMS (ESI) calcd. for  $(\text{C}_{16}\text{H}_{28}\text{O}_3 + \text{Na})^+$  292.1936, found 292.1934.



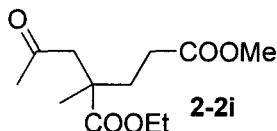
Compound **2-2g**: ethyl 2-methyl-2-(2-oxo-2-phenylethyl)pent-4-enoate

Colorless oil, 58%: IR (neat):  $\nu$  2926, 1733, 1685, 1456, 1224, 753  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.20-1.26 (m, 3H), 1.32 (s, 3H), 2.45-2.47 (m, 2H), 3.16 (d,  $J$  = 17.5 Hz, 1H), 3.41 (d,  $J$  = 17.5 Hz, 1H), 4.15 (q,  $J$  = 7.5 Hz, 2H), 5.06-5.10 (m, 2H), 5.75-5.81 (m, H), 7.45 (t,  $J$  = 7.5 Hz, 2H), 7.56 (t,  $J$  = 7.0 Hz, 1H), 7.93 (d,  $J$  = 8.0 Hz, 2H);  $^{13}\text{C}$ -NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.4, 22.4, 43.4, 43.7, 46.4, 60.7, 118.9, 128.1, 128.8, 133.3, 133.6, 137.4, 176.6, 197.8; GC/MS (EI)  $m/z$ : 261, 215, 187, 170, 141, 105, 77; Anal. Calcd. for  $\text{C}_{16}\text{H}_{20}\text{O}_3$ : C, 73.82; H, 7.74. Found: C, 73.97; H, 8.00.



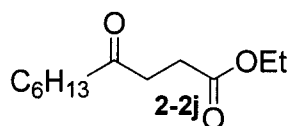
Compound **2-2h**: 1-ethyl 5-methyl 2-methyl-2-(2-oxooctyl)pentanedioate

Colorless oil, 92%: IR (neat):  $\nu$  2928, 2856, 1734, 1457, 1175  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.88 (t,  $J$  = 7.0 Hz, 3H), 1.22-1.31 (m, 12H), 1.53-1.56 (m, 2H), 1.82-1.87 (m, 1H), 1.92-1.98 (m, 1H), 2.27-2.37 (m, 4H), 2.55 (d,  $J$  = 17.5 Hz, 1H), 2.88 (d,  $J$  = 17.5 Hz, 1H), 3.67 (s, 3H), 4.13 (q,  $J$  = 7.0 Hz, 2H);  $^{13}\text{C}$ -NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.2, 14.3, 21.7, 22.7, 24.0, 29.0, 29.5, 31.8, 34.4, 43.0, 43.5, 51.0, 51.9, 60.9, 173.9, 176.0, 208.6; GC/MS (EI)  $m/z$ : 315, 269, 229, 201, 155, 85;



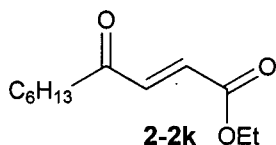
Compound **2-2i**: 1-ethyl 5-methyl 2-methyl-2-(2-oxopropyl)pentanedioate

Colorless oil, 80%: IR (neat):  $\nu$  2981, 2361, 1734, 1363, 1176, 1117, 1026  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.23-1.25 (m, 6H), 1.82-1.88 (m, 1H), 1.92-1.98 (m, 1H), 2.12 (s, 3H), 2.25-2.33 (m, 2H), 2.57 (d,  $J$  = 17.5 Hz, 1H), 2.92 (d,  $J$  = 17.5 Hz, 1H), 3.67 (s, 3H), 4.13 (q,  $J$  = 7.5 Hz, 2H);  $^{13}\text{C}$ -NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.3, 21.7, 29.5, 30.7, 34.3, 43.1, 51.8, 51.9, 61.0, 173.8, 176.0, 206.1; GC/MS (EI)  $m/z$ : 245, 200, 141, 113, 85; Anal. Calcd. for  $\text{C}_{12}\text{H}_{20}\text{O}_5$ : C, 59.00; H, 8.25. Found: C, 59.41; H, 8.41.



Compound **2-2j**: ethyl 4-oxodecanoate

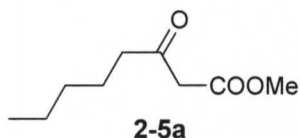
Colorless oil, 74%: IR (neat):  $\nu$  2929, 2858, 1735, 1373, 1187, 1033  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.88 (t,  $J$  = 6.5 Hz, 3H), 1.24-1.30 (m, 9H), 1.57-1.60 (m, 2H), 2.44 (t,  $J$  = 7.5 Hz, 2H), 2.57 (t,  $J$  = 6.5 Hz, 2H), 2.71 (t,  $J$  = 6.0 Hz, 2H), 4.12 (q,  $J$  = 7.0 Hz, 2H);  $^{13}\text{C}$ -NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.2, 14.4, 22.7, 24.0, 28.2, 29.1, 31.8, 37.2, 43.1, 60.8, 173.1, 209.5; GC/MS (EI)  $m/z$ : 215, 169, 144, 127, 113, 98, 85, 69.



Compound **2-2k**: (E)-ethyl 4-oxodec-2-enoate

Colorless oil, 74%: IR (neat):  $\nu$  2930, 2858, 1727, 1466, 1302, 1182, 1033  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.87 (t,  $J$  = 7.0 Hz, 3H), 1.25-1.33 (m, 9H), 1.61-1.64 (m, 2H), 2.62 (t,  $J$  = 7.0 Hz, 2H), 4.26 (q,  $J$  = 7.0 Hz, 2H), 6.66 (d,  $J$  = 16.5 Hz, 1H), 7.05 (d,  $J$  = 16.5 Hz, 1H);  $^{13}\text{C}$ -NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.2, 14.3, 22.7, 23.9, 29.0, 31.8, 41.8, 61.6, 130.9, 140.0, 165.8, 200.2; GC/MS (EI)  $m/z$ : 213, 169, 139, 127, 114, 97, 85, 69, 56; Anal. Calcd. for  $\text{C}_{12}\text{H}_{20}\text{O}_3$ : C, 67.89; H, 9.50. Found: C, 68.38; H, 9.79.

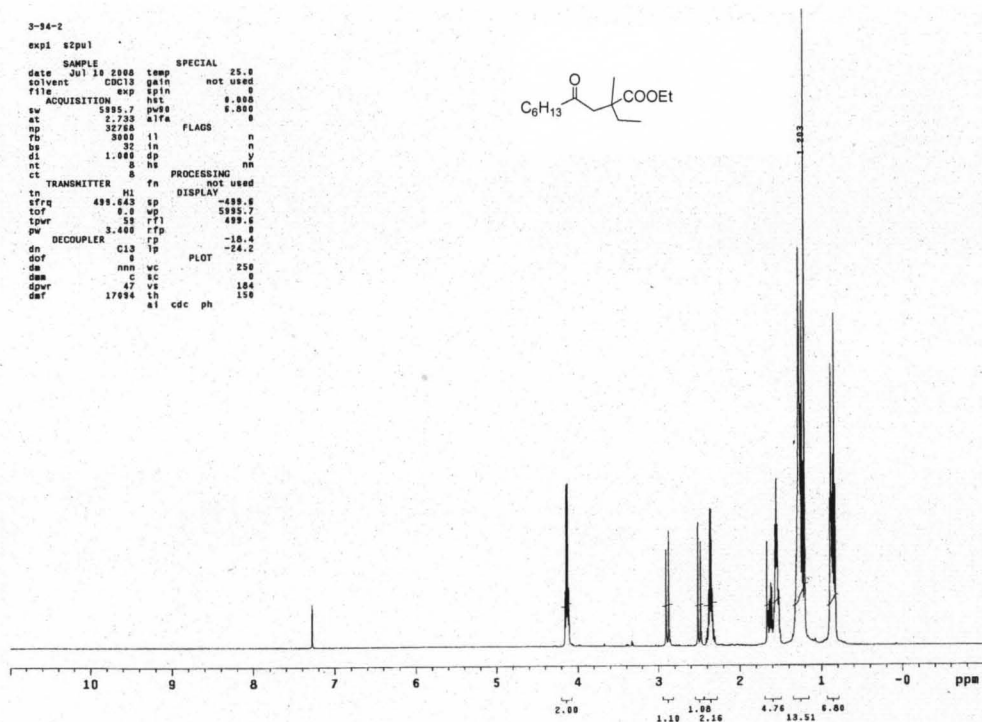
## Spectroscopic data of compounds 2-5.



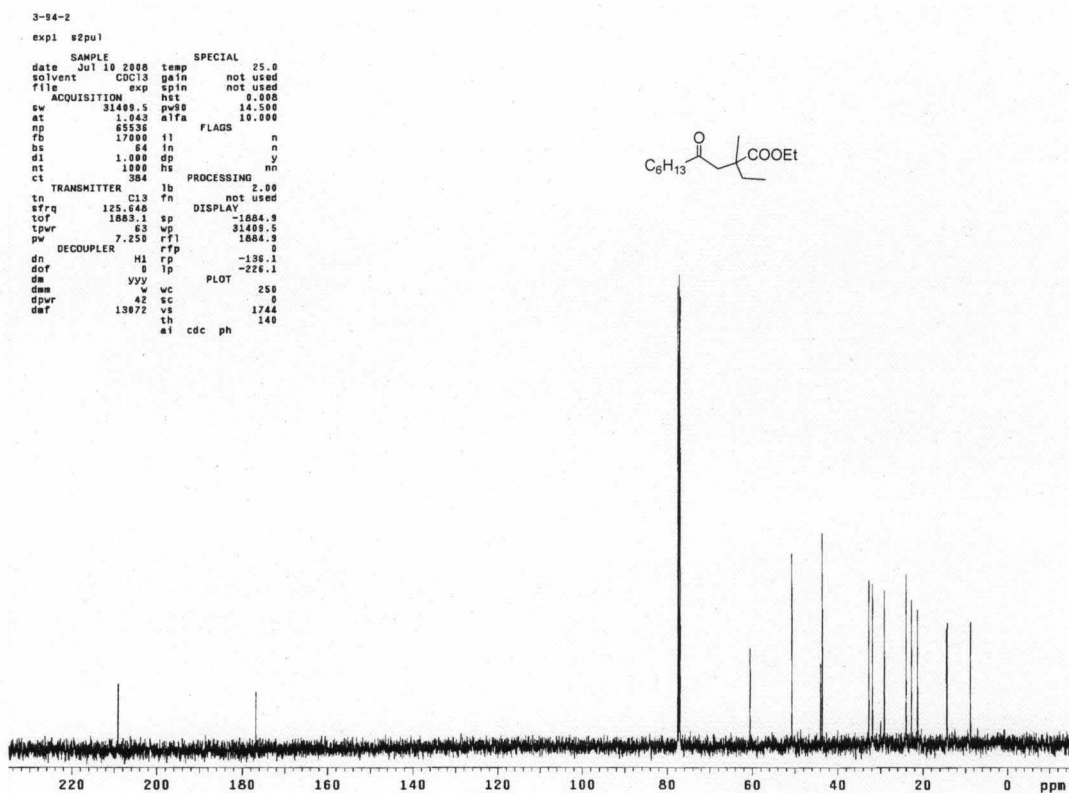
### Compound **2-5a**: methyl 3-oxooctanoate

Colorless oil, 76%: IR (neat):  $\nu$  2955, 2860, 2359, 1749, 1716, 1320, 1241, 1154, 1014  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.86 (t,  $J = 7.0$  Hz, 3H), 1.23-1.30 (m, 4H), 1.56-1.59 (m, 2H), 2.50 (t,  $J = 7.5$  Hz, 2H), 3.42 (s, 2H), 3.71 (s, 3H);  $^{13}\text{C}$ -NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.1, 22.6, 23.3, 31.3, 43.2, 49.2, 52.5, 167.9, 203.1; GC/MS (EI)  $m/z$ : 173, 130, 100, 40. GC/MS (EI)  $m/z$ : 269, 223, 195, 141, 113, 42. HRMS (ESI) calcd. for  $(\text{C}_9\text{H}_{16}\text{O}_3 + \text{Na})^+$  195.0997, found 195.0998.

### $^1\text{H}$ , $^{13}\text{C}$ spectras of compound 2-1a





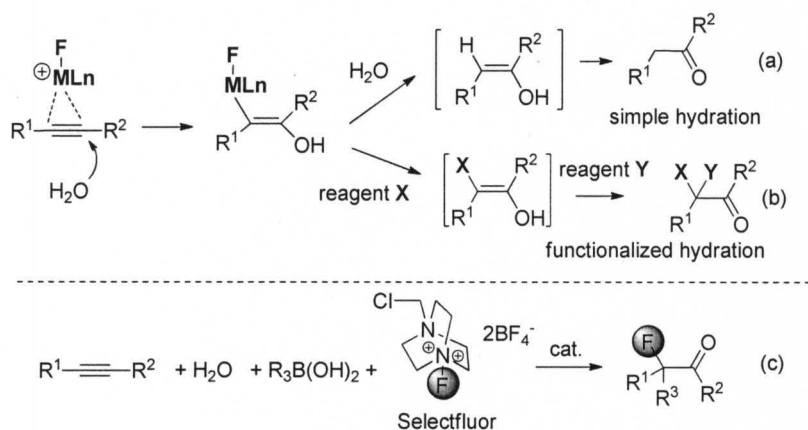


## CHAPTER 3. GOLD CATALYZED FUNCTIONALIZED HYDRATION OF ALKYNES

### 3.1 Functionalized hydration of alkynes

The hydration of alkynes is a straightforward and green method for preparing carbonyl compounds.<sup>54,95</sup> We used a gold-catalyzed synthesis of  $\gamma$ -keto esters through regioselective hydration of 3-alkynoate (see Chapter 2).<sup>96</sup> A major shortcoming of a transition metal catalyzed hydration is that it only adds the elements of H<sub>2</sub>O to an alkyne (Scheme 18-a).<sup>97-100</sup> We believed that the fluorine-enabled cationic gold catalyst could do more than simple hydration. We proposed that the vinyl metal complex hydration intermediate can react further with organoboronic acid (reagent X) and an electrophilic fluorine source such as Selectfluor (reagent Y) to give an  $\alpha,\alpha$ -disubstituted ketone (Scheme 18-b) in a one-pot reaction. We coined this process 'functionalized hydration'. A proof of principle is the synthesis of functionalized  $\alpha$ -fluoroketones—well-known targets and important synthetic intermediates.<sup>101-112</sup> Tertiary  $\alpha$ -fluorinated ketones have received much attention recently because compounds having an  $\alpha$ -fluorocarbonyl moiety are biologically active, they are effective mimics of  $\alpha$ -hydroxy ketones, useful probes in various biological processes, and enzyme inhibitors.<sup>101,103</sup> They also provide configurationally stable substituents for

molecules containing a tertiary chiral carbon atom next to a carbonyl group, an important structural motif in medicinal chemistry.<sup>103</sup> This one-pot tandem addition/oxidative coupling/fluorination sequence—using readily available starting materials (alkyne, water, organoboronic acid and Selectfluor)—would have clear advantages over literature methods, all of which require multiple synthetic steps.<sup>97-100</sup>



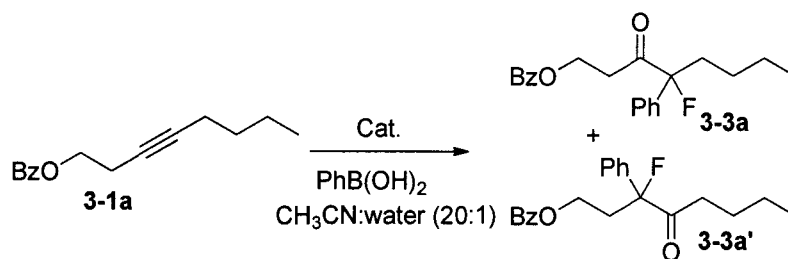
**Scheme 18.** Concept of functionalized hydration.

## 3.2 Results and discussion

We examined the reaction of **3-1a** with phenyl boronic acid (Table 4). Various metal catalysts were screened. Without additives, AuCl or Ph<sub>3</sub>PAuCl could not catalyze the reaction of **3-1** with phenyl boronic acid (Table 4, entries 1-2), but in combination with Selectfluor (1.5 equiv), we obtained 50% yield of **3-3** (Table 4, entry 4). Increasing the amount of Selectfluor further increases the yield (Table 4, entry 5, 6). Reducing the loading of Ph<sub>3</sub>PAuCl from 5% to 2% had no deleterious effect (Table 4, entry 7). Replacing Selectfluor with NFSi was not effective (Table 4, entry 8). We tested other gold(I) catalysts, but they were less

effective (Table 4, entries 9-11). We also tested gold(III) catalysts ( $\text{AuCl}_3$  and  $\text{AuCl}_3/\text{AgOTf}$ , Table 4, entries 12-13), but they gave much lower yields. Other transition metals like copper, silver or palladium could not catalyze this transformation under similar conditions (Table 4, entries 14-16). On exploring the scope of this novel functionalized hydration, we found that functionalized and unfunctionalized internal alkynes reacted with aryl boronic acid, giving very good yields of  $\alpha$ -substituted ketones, with moderate regioselectivity (Table 5, entries 1-12). Steric and electronic effects determined the regioselectivity.<sup>54,95</sup> For internal alkynes possessing a nucleophilic site nearby (e.g. the ester group in **3-1a**), this site may influence the regioselectivity through neighboring group participation.<sup>54,95,96</sup>

**Table 4. Functionalized hydration: screening of conditions**



entries <sup>a</sup>	Catalysts	Selectfluoro/equiv	yields (3-3a:3-3a')
1	AuCl	none	no reaction
2	PPh <sub>3</sub> AuCl	none	no reaction
3	PPh <sub>3</sub> AuCl	0.1	no reaction
4	PPh <sub>3</sub> AuCl	1.5	50 (5.1 : 1)
5	PPh <sub>3</sub> AuCl	2.2	57 (4.7:1)
6	PPh <sub>3</sub> AuCl	2.5	84 (6.7:1)
7 <sup>b</sup>	PPh <sub>3</sub> AuCl	2.5	83 (5.7:1)
8 <sup>c</sup>	PPh <sub>3</sub> AuCl	2.5	no reaction
9	P(o-Tol) <sub>3</sub> AuCl	2.5	75 (6.5:1)
10	P(p-CF <sub>3</sub> -Ph) <sub>3</sub> AuCl	2.5	78 (5.0:1)
11	AuCl	2.5	65 (4.7:1)
12	AuCl <sub>3</sub>	2.5	41 (5.7:1)
13	AuCl <sub>3</sub> /AgOTf(15%)	2.5	29 (5.6:1)
14	CuBr	2.5	complex mixture
15	AgOTf	2.5	complex mixture
16	PdCl <sub>2</sub>	2.5	complex mixture

<sup>a</sup>5 % catalyst, rt for 18h; <sup>b</sup>2 % catalyst, rt for 24 h; <sup>c</sup> use NFSI in stead of selectfluoro. Selectfluoro: 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]-octane bis(tetrafluoroborate). NFSi: N-Fluorobenzenesulfonimide.

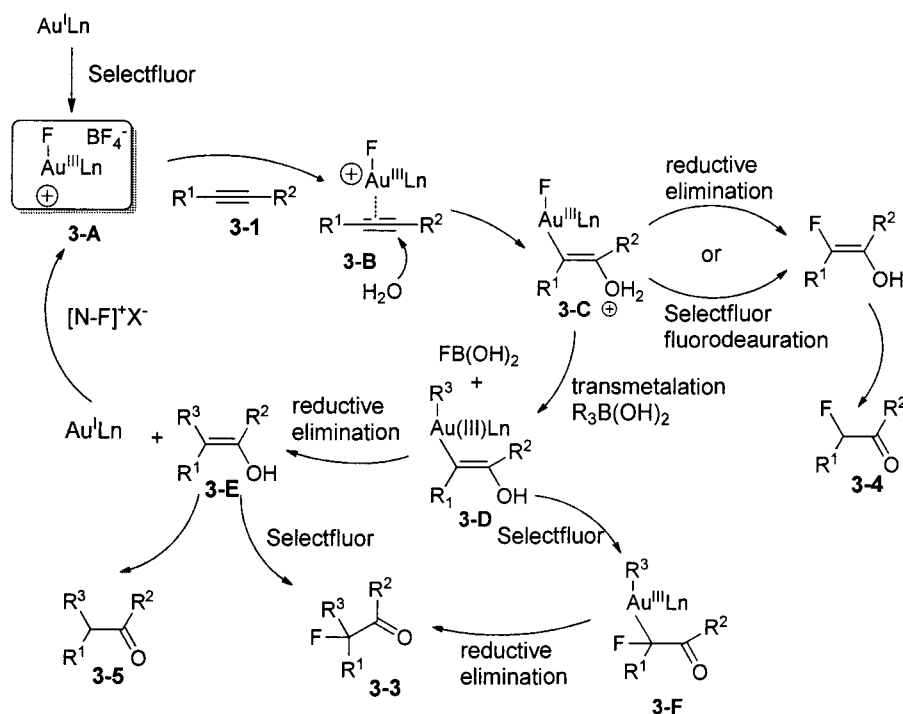
**Table 5. Scope of the functionalized hydration.**

$  \begin{array}{c}  \text{R}^1\text{---}\text{C}\equiv\text{C}\text{---}\text{R}^2 \\  \text{3-1}  \end{array}  \xrightarrow[\text{CH}_3\text{CN:water (20:1) rt}]{\text{ClAu(PPh}_3)_2 \text{ 5\%}}  \begin{array}{c}  \text{R}^3\text{B(OH)}_2 \text{ (3-2), Selectfluor} \\  \text{F} \\  \text{R}^1\text{---}\text{C}\text{---}\text{C(=O)R}^2 \\  \text{R}^3  \end{array}  $			
entries	3-1	3-2 (R <sup>3</sup> B(OH) <sub>2</sub> )	products
1		PhB(OH) <sub>2</sub> 3-2a	  <b>3-3a, 88% (6.7:1)</b>
2		3-2a	  <b>3-3b, 88% (4.6:1)</b>
3		3-2a	 <b>3-3c, 63%</b>
4		3-2a	 <b>3-3d, 79%</b>
5		3-2a	  <b>3-3e, 85% (2.2:1)</b>
6		3-2a	  <b>3-3f, 47% (2.1:1)</b>
7		3-2a	  <b>3-3g, 83% (5:1)</b>
8		3-2a	  <b>3-3h, 70% (5.0:1)</b>
9	3-1a	<i>p</i> -F-C <sub>6</sub> H <sub>4</sub> -B(OH) <sub>2</sub> 3-2b	  <b>3-3i, 88% (5.3:1)</b>
10	3-1a	<i>m</i> -Cl-C <sub>6</sub> H <sub>4</sub> -B(OH) <sub>2</sub> 3-2c	  <b>3-3j, 71% (3.4:1)</b>
11	3-1a	<i>p</i> -Me-C <sub>6</sub> H <sub>4</sub> -B(OH) <sub>2</sub> 3-2d	  <b>3-3k, 88% (6.7:1)</b>
12	3-1a	<i>p</i> -Ph-C <sub>6</sub> H <sub>4</sub> -B(OH) <sub>2</sub> 3-2e	  <b>3-3l, 90% (5.3:1)</b>

### 3.3 Mechanistic studies

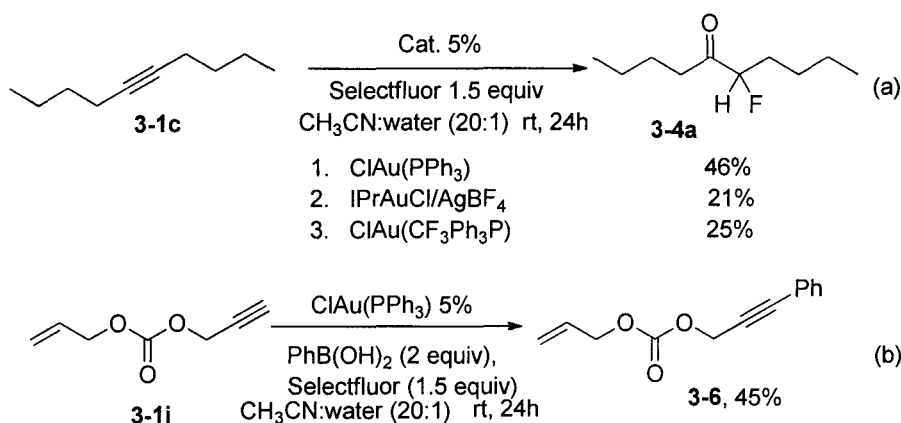
Our proposed mechanism, (shown in Scheme 19), takes its cue from the reaction of boronic acid with alkynes.<sup>113-128</sup> Initially, water attacks the gold-activated alkyne **3-B** to form a vinyl gold complex **3-C**,<sup>129</sup> which then reacts with a metal reagent RM (e.g., PhB(OH)<sub>2</sub>) through a transmetalation process, to give intermediate **3-D**. We believe that the strong B-F bond and the weak Au-F bond are the driving forces behind this transmetalation. Reductive elimination of **3-D** gives **3-E**. The reaction doesn't stop at this stage; instead **3-E** can be fluorinated by Selectfluor to give the functionalized ketone **3-3**.<sup>130</sup> Because we never isolated **3-5** in any cases, it is possible that intermediate **3-D** reacts with Selectfluor first to give **3-F**, Following reductive elimination gives the final product **3-3**. The transmetalation of Au<sup>I</sup>-Cl complex with boronic acid has been demonstrated by Hashmi and coworkers in a recent paper.<sup>131</sup> The transmetalation of Au-F with boronic acid has also been proposed by Zhang and co-workers in their gold catalyzed cross-coupling reaction of propargylic acetate.<sup>34</sup> To probe the proposed mechanism in Scheme 19. We conducted two control experiments (Scheme 20). According to Scheme 19, fluoroketones **3-4** could be formed in the absence of a coupling partner R<sub>3</sub>M, in which case, the vinyl metal complex **3-C** undergoes reductive elimination or fluorodemetalation<sup>15</sup> to give fluoroketone **3-4**. This was found experimentally, although only moderate yields have been obtained (Scheme 20-a). The reaction of terminal alkyne **3-1i** gives the oxidative coupling product **3-6**.<sup>132</sup> The formation of **3-6** hints towards a tandem mechanism

that may involve the following steps: fluorination of the gold complex, transmetalation with boronic acid, and reductive elimination, as shown in (Scheme 21). It may be possible that a base-promoted deprotonation of a terminal alkyne, whose acidity has increased due to gold complexation, could account for the formation of alkynyl gold intermediate **3-G**. The formation of alkynyl gold complex through desilylation has been reported by Russell and co-workers recently.<sup>133</sup> It is interesting to note that gold catalysts undergo transmetalation and reductive elimination readily, although they are not able to undergo oxidative addition—as Pd does in coupling reactions.

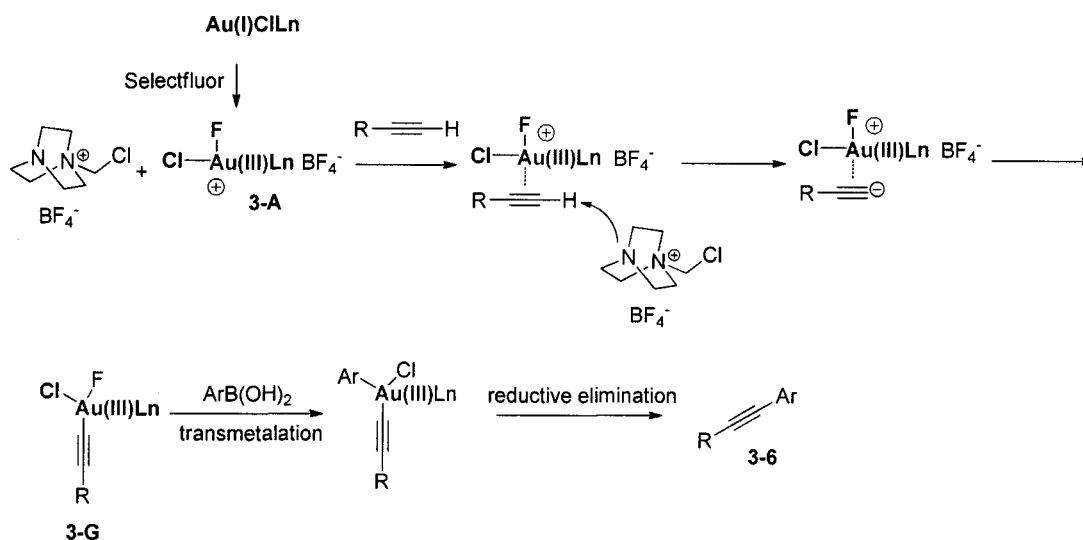


**Scheme 19. Proposed mechanism for the functionalized hydration.**





**Scheme 20. Synthesis of fluoroketones and oxidative coupling of alkynes.**

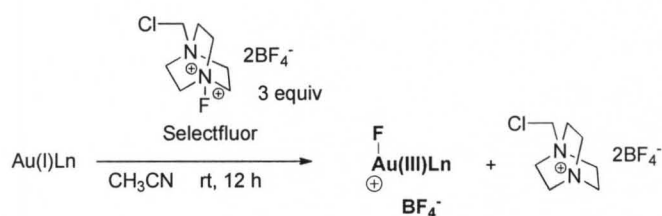


**Scheme 21. Mechanism for the formation of 3-6.**

### 3.4 Mechanistic study of gold (III) species using X-ray photoelectron spectroscopy

X-ray photoelectron spectroscopy (XPS) is a quantitative spectroscopic technique that can be used to measure the chemical or electronic state of an element from Li to U, empirical formula of pure materials, uniformity of elemental composition.<sup>134</sup> XPS spectra are obtained by irradiating a material with a beam of X-rays while simultaneously measuring the kinetic energy and number of electrons that escape from the top 1 to 10 nm of the material being analyzed.

That collection of spectra yielded peaks with binding energies (reported as BEs) that are characteristic for each specific element. Tables of binding energies (BEs) that identify the shell and spin-orbit of each peak produced by a given element are included with modern XPS instruments, and can be found in various handbooks. Because these experimentally determined BEs are characteristic of specific elements, they can be directly used to identify experimentally measured peaks of a material with unknown elemental composition. For the same element, different chemical states have the different BEs, For example, it has been used in the determination of the chemical states of supported gold catalysts.<sup>135</sup> The binding energy (BE) of Au 4f<sub>7/2</sub> electron of each gold oxidation states are usually different enough to allow differentiation.<sup>134</sup>



Au(I)Ln = AuCl, ClAuPPh<sub>3</sub>

**Scheme 22. Preparation of gold complex samples.**

**Table 6. The literature reports of binding energy of Au 4f<sub>7/2</sub> electron.**

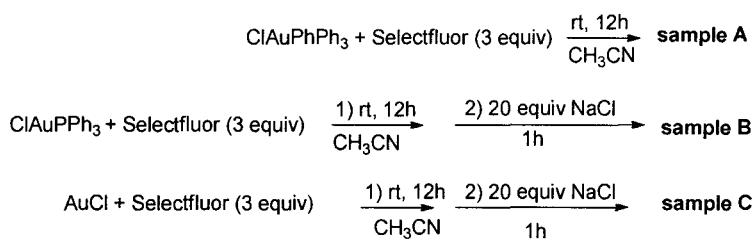
Sample	Au(0)	ClAu(I)PPh <sub>3</sub>	ClAu(I)(PPh <sub>3</sub> ) <sub>2</sub>	Cl <sub>3</sub> Au(III)PPh <sub>3</sub>
Au 4f <sub>7/2</sub> BE (eV)	84.0±0.1	85.4	85.4	87.3

We collect the X-ray photoelectron spectroscopy spectra by a XPS spectrometer from Thermo Fisher Scientific, equipped with a standard Al K<sub>α</sub> excitation source (1486.6 eV). Gold complex standards (ClAuPPh<sub>3</sub> and NaAuCl<sub>4</sub>) were sampled as powders and pressed on a double-sided adhesive carbon tape. Gold catalysts

samples were sampled as solution and dried in normal atmosphere on a double-sided adhesive carbon tape. The binding energy (BE) scale was calibrated by measuring C 1s peak (BE = 284.6 eV). A non-linear least-square peak fitting routine was used for the analysis of XPS spectra, separating elemental species in different oxidation states. The curve fitting of the Au 4f core-level spectrum is performed by using two spin-orbit split Au 4f<sub>7/2</sub> and Au 4f<sub>5/2</sub> components, separated by 3.67 eV, in a fixed intensity ratio.

In our proposed mechanism, the low valence gold(I) complex first reacts with Selectfluor to generate a high valence gold(III) complex, which activates the alkyne towards nucleophilic attack (Scheme 22). In order to test this mechanism, first we tested our gold standard samples (ClAu<sup>I</sup>PPh<sub>3</sub> and NaAu<sup>III</sup>Cl<sub>4</sub>), the Au 4f<sub>7/2</sub> photoelectron peak is located at a BE values of 85.7 and 87.6 eV respectively (Figure 3), which is quite consistent with the literature (Table 6).<sup>134</sup> Our preliminary XPS study show that gold complexes like AuCl and AuCl<sub>3</sub> without suitable ligands are not stable under the conditions used in XPS measurements (e.g. high vacuum). Here we used the halides to react with gold (III) to give the more stable chloroaurate or bromoaurate (Scheme 23). We prepared our samples A-C using the same conditions as the standards (Figure 3). Sample A appeared as a mixture of two gold oxidation states (BE of Au 4f<sub>7/2</sub> = 84.4, 87.5 eV). We then tested the chloride stabilized sample B (BE of Au 4f<sub>7/2</sub> = 84.2, 87.6 eV), sample C (BE of Au 4f<sub>7/2</sub> = 84.4, 87.1 eV); they gave similar patterns but with higher percentage of gold(III) species. Because the gap between Au4f peak of two gold states is large (ca 3.0 eV), we assigned them as Au<sup>0</sup> and Au<sup>III</sup> species,

respectively. The chloride stabilized samples B and C show a very similar pattern, but with higher percentage of gold(III) species. Our XPS measurements confirm the existence of gold(III) (BE of Au 4f<sub>7/2</sub> = 87.6 eV) in the reaction mixture of gold(I) catalyst and Selectfluor (Figure 3). The existence of gold(0) can be explained by disproportionation of unreacted Au<sup>I</sup> complex or decomposition/reduction of Au<sup>III</sup> species in high vacuum during XPS measurements. Because Au<sup>III</sup> species are the major components in all tests, the existence of Au<sup>III</sup> species can't attributed to disproportionation of unreacted Au<sup>I</sup> complexes alone. Because the bonding energy of gold(0) and gold(I) are close (the difference is ca. 1 eV), and mean measurement error of XPS is around 0.5 eV. It is very possible than all the sample contains certain amount of unreacted gold(I) species, especially in sample B.



**Scheme 23. Conversion of cationic gold (III) intermediate to chloroaurate or bromoaurate.**

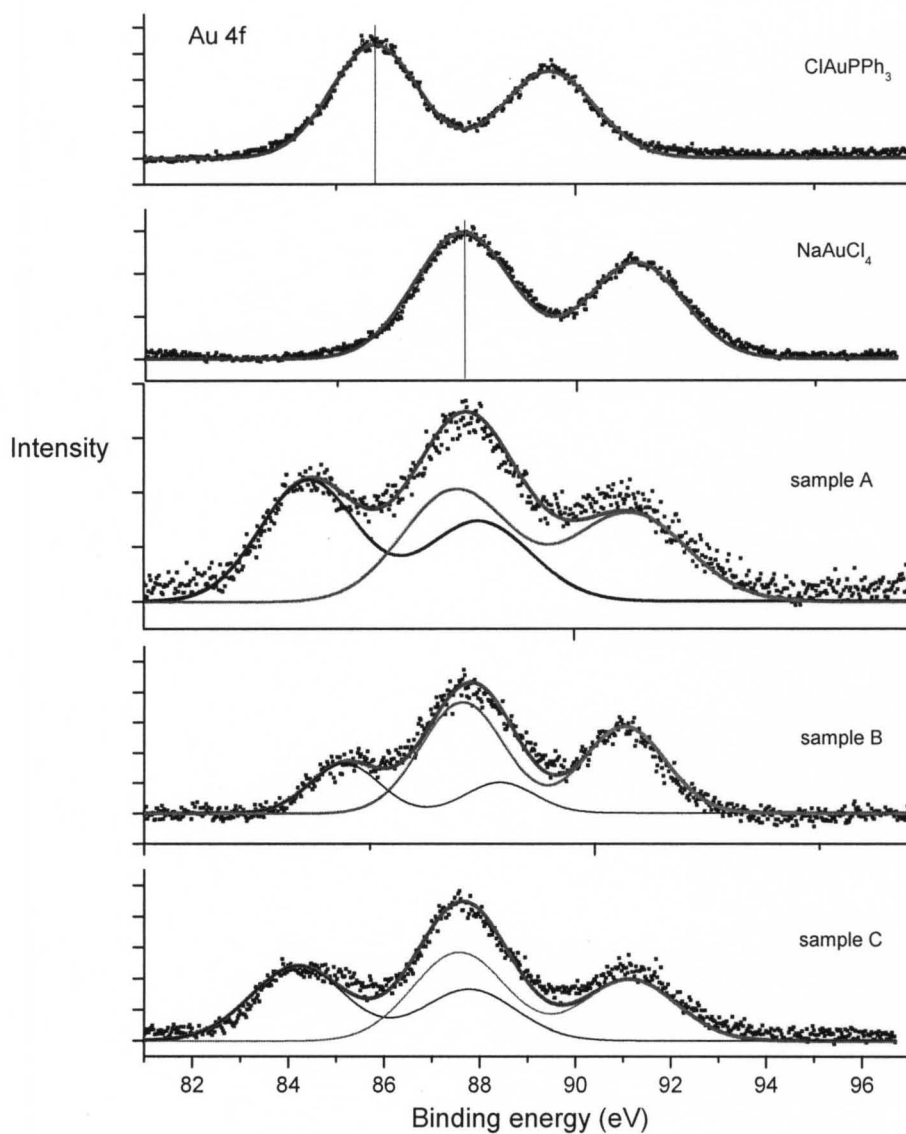


Figure 3. XPS curve fitting of the Au 4f photoelectron peaks.

### 3.5 Monitoring the progress of the reaction using $^{19}\text{F}$ -NMR

Our XPS measurements indicate the existence of gold (III) species, but XPS experiments can only be conducted in vacuum in the solid state. In order to investigate the reaction in solution phase, we monitored the progress of the reaction using  $^{19}\text{F}$ -NMR (Figure 4). Our preliminary experiments showed that

Selectfluor did react with gold(I) complex at room temperature. For example, after addition of Selectfluor to AuCl in CD<sub>3</sub>CN, a new peak (bs, -184 ppm) appeared and its intensity increased with time (Figure 4-1, 4-2). When we added PhB(OH)<sub>2</sub> to the system, this peak disappeared immediately and biphenyl was detected by TLC 10 min after PhB(OH)<sub>2</sub> was added (Figure 4-3). And chromatographic separation and comparison of NMR with authentic sample indicate biphenyl is indeed generated in these transformations. This suggests that the new peak represents a reactive metal fluoride species, which we tentatively assigned as [Au<sup>III</sup>ClFLn]<sup>+</sup> (Ln = CH<sub>3</sub>CN). The formation of FB(OH)<sub>2</sub> has been proposed by Toste and co-workers in transmetalation of gold intermediate,<sup>136</sup> but we don't have the authentic sample to compare the NMR, so we tentatively assign the peak at -149 ppm as FB(OH)<sub>2</sub>. The formation of biphenyl could be rationalized by transmetalation with phenylboronic acid in a first stage, the second equivalent of phenyl boronic acid could replace the BF<sub>4</sub><sup>-</sup> or the chloride in a manner that is still the subject of discussion, and this would be followed by reductive elimination to give biphenyl (Figure 4 top). This high reactivity rules out the possibility that it is a simple fluoride anion. Ph<sub>3</sub>PAuCl can also be oxidized under the same conditions but at a slower rate; however, in this case the phosphine ligand Ph<sub>3</sub>P was also oxidized (by the high valence gold or Selectfluor), after prolonged times. Ph<sub>3</sub>P=O was detected in the reaction mixture (confirmed by <sup>31</sup>P-NMR and ESI-MS).<sup>34,43</sup>

At this time, for formation of biphenyl, we could not rule out the possibility of other mechanism like radical mechanism, which is also a common process for organoboronic acids.

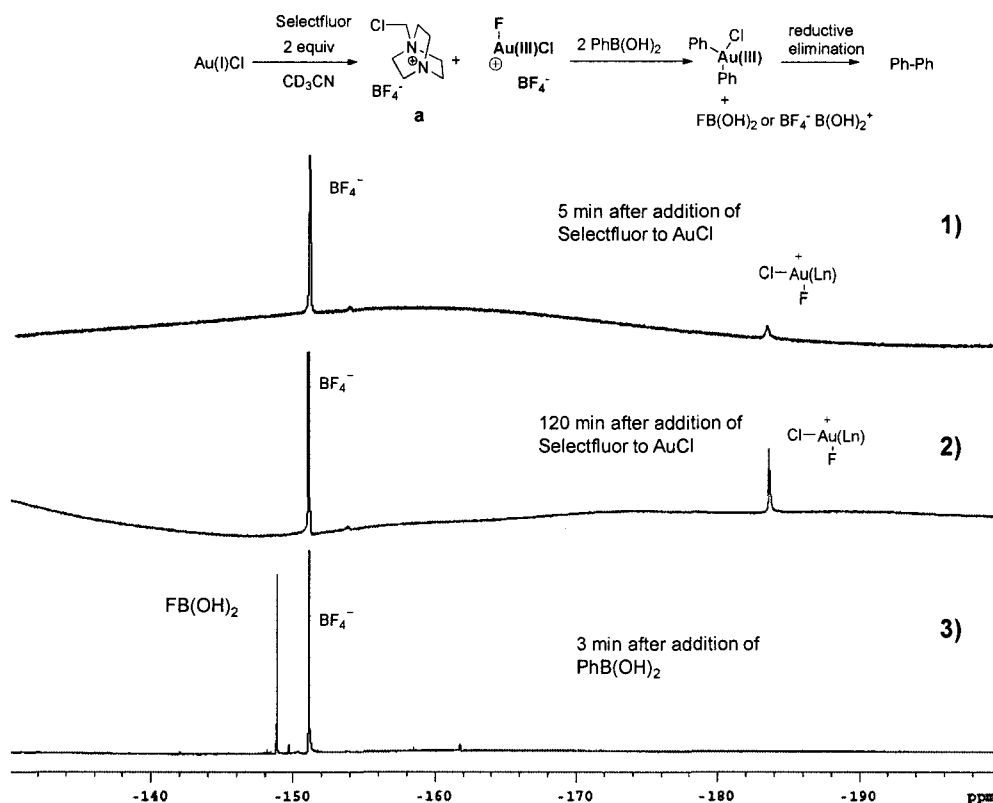
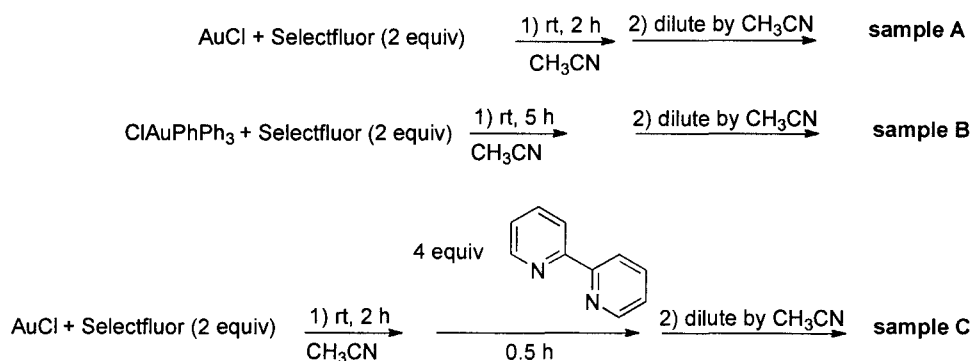


Figure 4. Monitoring the reaction of AuCl with Selectfluor using <sup>19</sup>F-NMR (Ln = CH<sub>3</sub>CN).

### 3.6 Electrospray ionization mass spectrometry (ESI-MS). Identification of cationic Au(III) species

Electrospray ionization mass spectrometry (ESI-MS) has become an important tool in the identification of labile reaction intermediates. An advantage of ESI-MS is that it allows direct sampling from the reaction mixture, and because many of our gold intermediates are charged species, ESI-MS could help us to detect charged species. We conducted a high-resolution ESI-MS investigation of the

cationic or anionic species in the catalytic system. First, we checked the high-resolution ESI-MS spectra of samples A and B (Scheme 24, Sample A, B) but only Au(I) species (peaks **c**, **d**, **f**) and reduced Selectfluor (peak **b**) were detected (Figure 5) and we could not detect a Au(III) species. Because a Au(III) complex has a square-planar geometry, a bidentate ligand should greatly stabilize this Au(III) complex, which in turn, could be easier to detect by ESI-MS spectrometry. Hence, we added excess amounts of bipyridine to the reaction mixture (Scheme 24, sample C). The high-resolution ESI-MS spectrum is shown in Figure 6 and Figure 7.



**Scheme 24. Preparation of samples for ESI-MS study.**



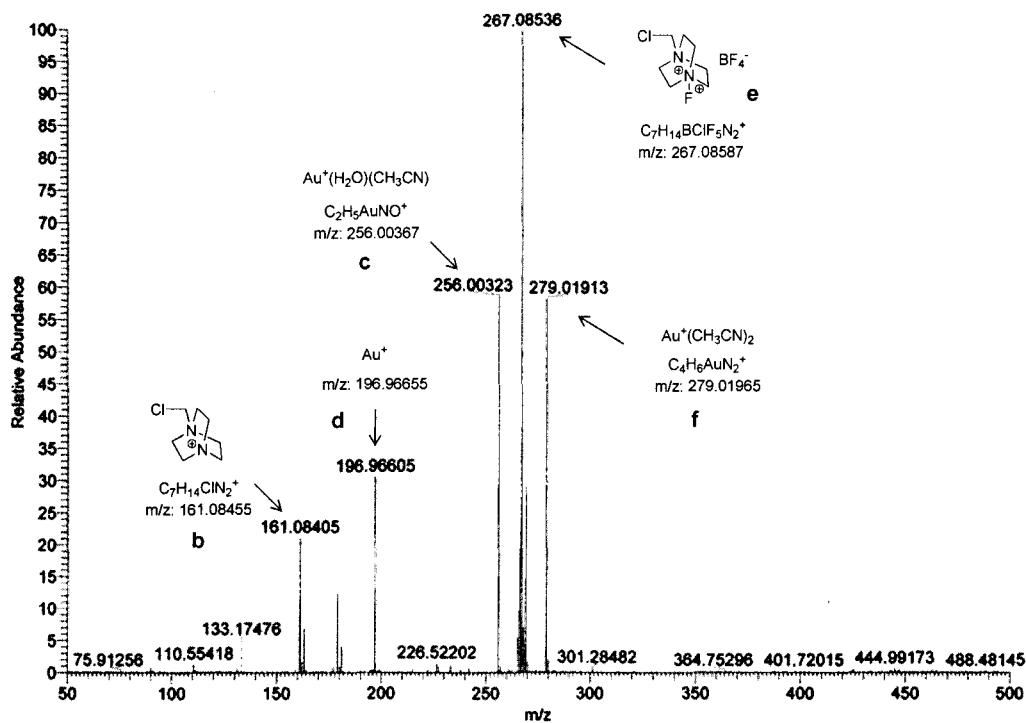


Figure 5. ESI-MS of sample A.

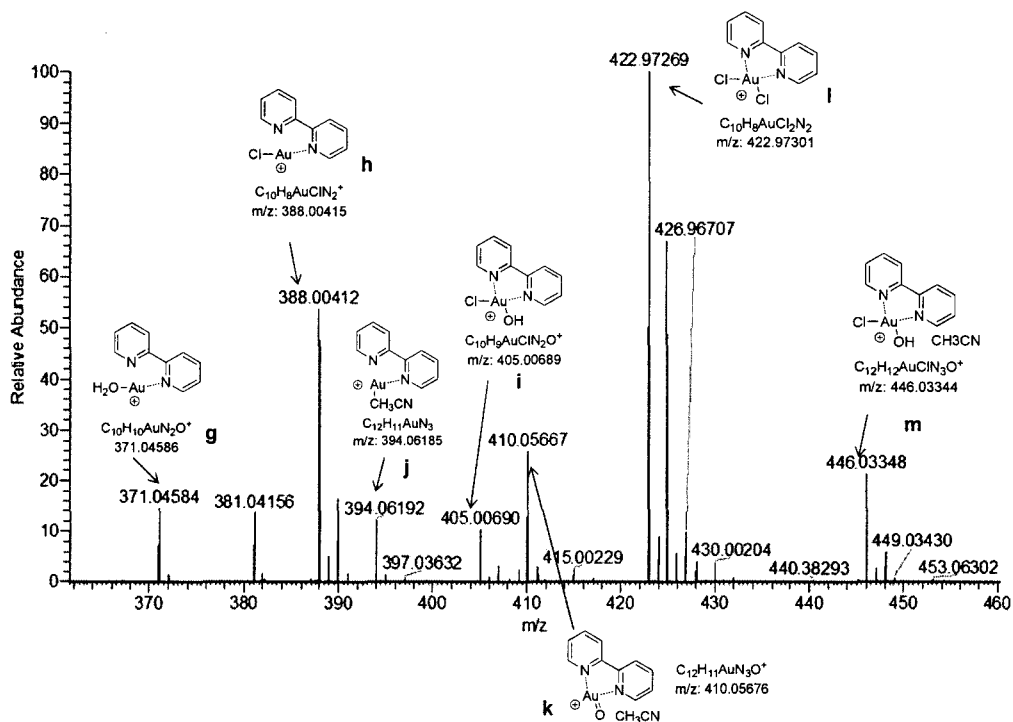
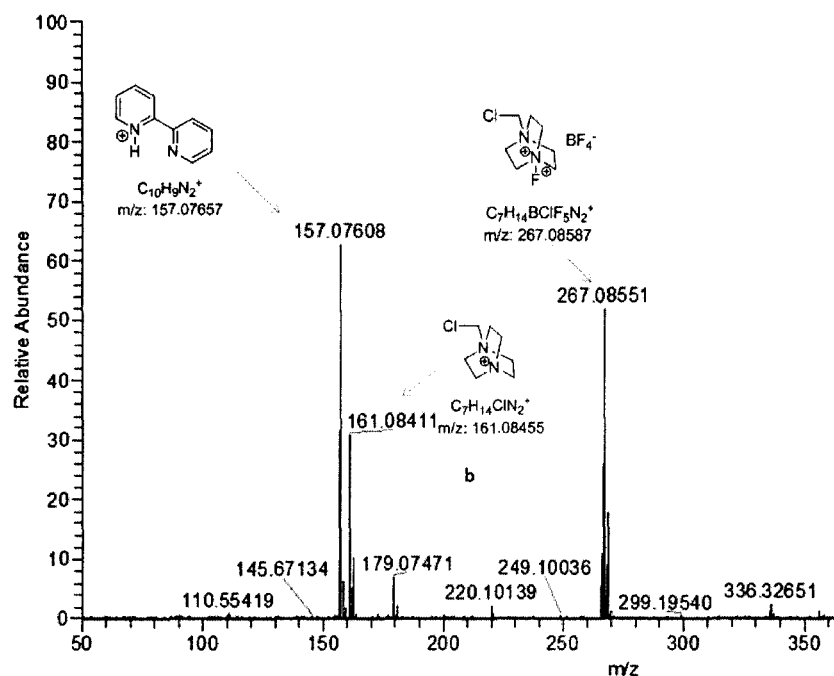
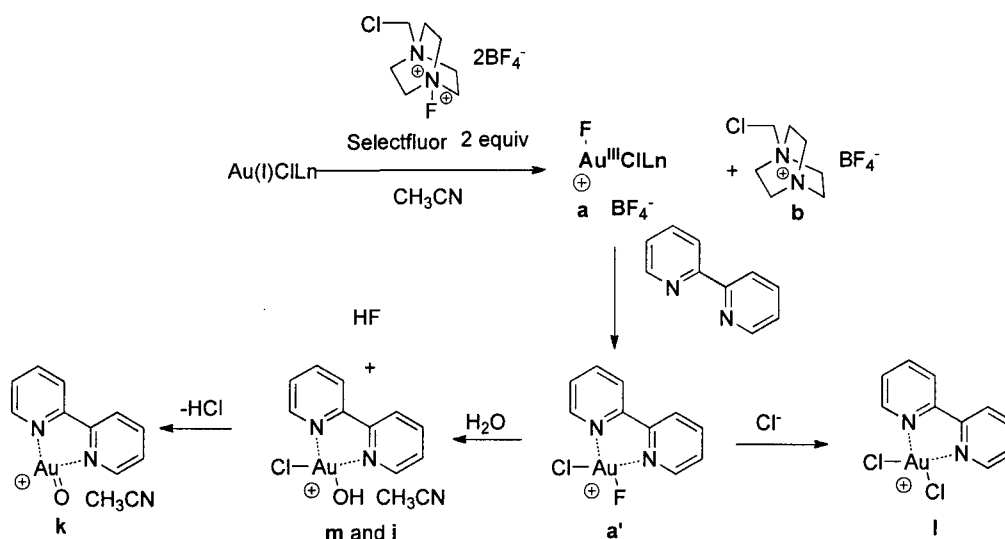


Figure 6. ESI-MS of sample C (part 1, m/z 360-460).



**Figure 7. ESI-MS of sample C (part 2, m/z from 50 to 360).**

In Figure 6, various cationic Au(III) species were detected (peaks i, k, l, m), but  $[Au(III)ClF]^+$  itself was not detected; this may be due to the fact that metal-fluorine bonds tend to be labile and reactive. Indeed, gold(I) fluoride, was once thought impossible to prepare. Compared to many other metal fluorine bonds, Au-F is a weaker bond. So, under the ESI-MS conditions (high temperature during the electrospray ionization),  $[Au(III)ClF]^+$  (a) may lose fluorine and pick up chloride from other gold complexes or  $OH^-$  from trace amounts of water in the system, because both chloride and hydroxyl have much stronger affinity to gold (Scheme 25).



**Scheme 25. Mechanism for the formation of gold(III) species in Figure 6.**

### 3.7 Summary and future directions

In sum, a potentially new role for fluorine in cationic gold catalysis was proposed, an example of which is the functionalized hydration of alkynes to give  $\alpha$ -substituted- $\alpha$ -fluoroketones, in one pot and under mild conditions. The ready availability of alkynes and organoboronic acids, and the current interest in  $\alpha$ -fluoroketones makes this reaction quite attractive. The broader implications of cationic metal species enabled by fluorine are currently under study in our laboratory.

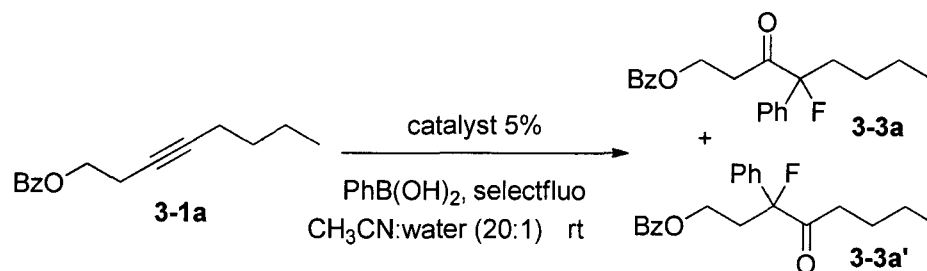
### 3.8 Experimental

#### General

$^1\text{H}$ ,  $^{13}\text{C}$  and  $^{19}\text{F}$  NMR spectra were recorded at 500, 126 and 470 MHz respectively, using  $\text{CDCl}_3$  as a solvent. The chemical shifts are reported in  $\delta$  (ppm) values relative to  $\text{CHCl}_3$  ( $\delta$  7.26 ppm for  $^1\text{H}$  NMR and  $\delta$  77.0 ppm for  $^{13}\text{C}$  NMR) and  $\text{CFCl}_3$  ( $\delta$  0 ppm for  $^{19}\text{F}$  NMR), multiplicities are indicated by s (singlet),

d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), m (multiplet) and br (broad). Coupling constants,  $J$ , are reported in Hertz. Coupling constants are reported in hertz (Hz). All air and/or moisture sensitive reactions were carried out under argon atmosphere. Solvents (tetrahydrofuran, ether, dichloromethane and DMF) were chemically dried using a commercial solvent purification system. All other reagents and solvents were employed without further purification. The products were purified using a Biotage flash+ system or Chromatotron apparatus or a regular glass column. TLC was developed on Merck silica gel 60 F254 aluminum sheets. Elemental analysis was performed at Atlantic Microlabs Inc., Norcross, Georgia 30091. High resolution ESI-MS were obtained using a MS-FTICR-MS<sup>n</sup> system (LTQ FT, Thermo Electron Corp.) at the CREAM Mass Spectrometry Facility, University of Louisville, Kentucky. When needed, reactions were monitored using <sup>19</sup>F NMR and the mixture percentage yield was obtained using  $\alpha,\alpha,\alpha$ -trifluoromethylbenzene as internal reference.

### General procedure for preparation of 3-3.

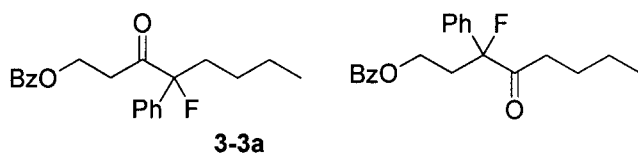


Selectfluor (354 mg, 1.0 mmol, 2.5 equiv) was added to a solution of the alkyne **3-1a** (92 mg, 0.4 mmol), Ph<sub>3</sub>PAuCl (9.8 mg, 0.02 mmol, 5% equiv) and phenylboronic acid (98 mg, 0.8 mmol, 2 equiv) in 3 mL MeCN:H<sub>2</sub>O (20:1). The reaction was stirred at the room temperature for 18 h. The reaction mixture was

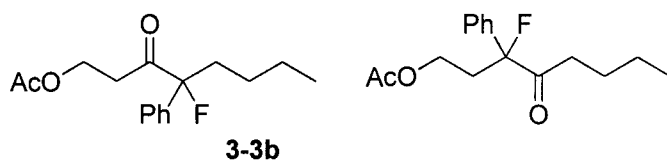
quenched with saturated  $\text{NH}_4\text{Cl}$  solution, the resulting aqueous mixture was extracted by diethyl ether (15 mL x 3), and then the combined organic layer was dried over  $\text{Na}_2\text{SO}_4$ . The solvent was removed under reduced pressure to give crude product, the crude product was purified by flash silica gel chromatography (30% dichloromethane in hexane – 60% dichloromethane in hexane) to give the product **3-3a** as a mixture of two regioisomer (**3-3a**: **3-3a'** = 6.7: 1) 118 mg (88%).

### Spectroscopic data of compounds 3-3

**3-3a**: 4-fluoro-3-oxo-4-phenyloctyl benzoate, 3-fluoro-4-oxo-3-phenyloctyl benzoate

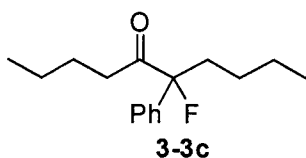


IR (neat):  $\nu$  2958, 1724, 1450, 1275, 1116, 711  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ), Major isomer:  $\delta$  0.87 (t,  $J$  = 6.5 Hz, 3H), 1.29-1.31 (m, 4H), 2.03-2.18 (m, 1H), 2.22-2.38 (m, H), 3.08-3.1 (m, 2H), 4.55 (t,  $J$  = 6 Hz, 2H), 7.31-7.53 (m, 8H), 7.82 (d,  $J$  = 7.5 Hz, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ), major isomer:  $\delta$  14.0, 22.8, 22.5, 36.6, 37.8 (d,  $J$  = 22 Hz), 59.4, 103.5 (d,  $J$  = 186 Hz), 124.5 (d,  $J$  = 10.5 Hz), 128.4, 128.8, 129.7, 133.1, 137.6 (d,  $J$  = 22 Hz), 166.4, 208.5 (d,  $J$  = 30 Hz);  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ ): Major isomer:  $\delta$  -170.04 (t,  $J$  = 25.4 Hz); GC/MS (EI)  $m/z$ : 221, 201, 177, 135, 77; Anal. Calcd. for  $\text{C}_{21}\text{H}_{23}\text{FO}_3$ : C, 73.66; H, 6.77. Found: C, 73.42; H, 6.75.



**3-3b:** 4-fluoro-3-oxo-4-phenyloctyl acetate, 3-fluoro-4-oxo-3-phenyloctyl acetate

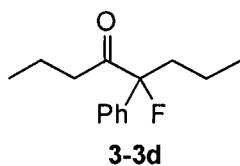
colorless oil, 88% , obtained as a mixture of two regioisomers in ratio of 4.6: 1. IR (neat):  $\nu$  2959, 1744, 1366, 1237, 1038, 700  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ), major isomer:  $\delta$  0.81-0.89 (m, 3H), 1.19-1.34 (m, 4H), 1.9 (s, 3H), 2.05-2.15 (m, H), 2.18-2.29 (m, H), 2.85-2.91 (m, H), 2.96-3.03 (m, H), 4.23-4.33 (m, 2H), 7.33-7.44 (m, 5H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ), major isomer:  $\delta$  14.0, 20.9, 22.8, 25.1, 36.6, 37.7 (d,  $J$  = 21 Hz), 58.9 (d,  $J$  = 2 Hz), 102.8 (d,  $J$  = 186 Hz), 124.5 (d,  $J$  = 10.0 Hz), 128.4, 128.7, 137.6 (d,  $J$  = 22 Hz), 170.9, 206.8 (d,  $J$  = 30.0 Hz);  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ ): major isomer:  $\delta$  -169.95 (t,  $J$  = 24.9 Hz); GC/MS (EI)  $m/z$ : 221, 201, 165, 145, 135, 109, 85; Anal. Calcd. for  $\text{C}_{16}\text{H}_{21}\text{FO}_3$ : C, 68.55; H, 7.55. Found: C, 69.31; H, 7.67.



**3-3c:** 6-fluoro-6-phenyldecan-5-one

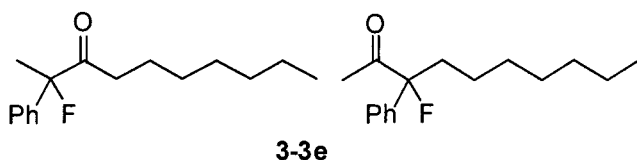
colorless oil, 63%, IR (neat):  $\nu$  2958, 2872, 1723, 1448, 699  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.83-0.96 (m, 6H), 1.21-1.34 (m, 6H), 1.44-1.54 (m, 2H), 2.05-2.13 (m, 1H), 2.19-2.51 (m, 1H), 2.51-2.58 (m, 1H), 2.65-2.71 (m, 1H), 7.30-7.33

(m, 1H), 7.36-7.39 (m, 2H), 7.43-7.45 (m, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  13.9, 14.0, 22.3, 22.9, 25.2, 25.3, 37.2, 37.9, (d,  $J = 21$  Hz), 103.6 (d,  $J = 186$  Hz), 124.5, 128.2, 128.6, 138.3 (d,  $J = 22$  Hz), 209.9 (d,  $J = 29$  Hz);  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ ):  $\delta$  -169.52 (t,  $J = 24.9$  Hz); GC/MS (EI)  $m/z$ : 231, 165, 145, 109, 85, 57; Anal. Calcd. for  $\text{C}_{16}\text{H}_{23}\text{FO}$ : C, 76.76; H, 9.26. Found: C, 76.74; H, 9.28.



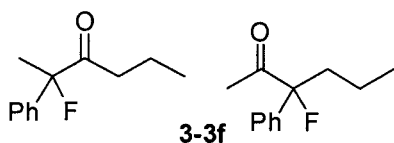
**3-3d** : 5-fluoro-5-phenyloctan-4-one

colorless oil, 79%, IR (neat):  $\nu$  2963, 2875, 1724, 1448, 758,  $700\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.83 (t,  $J = 7.5$  Hz, 3H), 0.91 (t,  $J = 7.5$  Hz, 3H), 1.28-1.35 (m, 2H), 1.48-1.60 (m, 2H), 2.01-2.11 (m, 1H), 2.16-2.26 (m, 1H), 2.50-2.56 (m, 1H), 2.63-2.69 (m, 1H), 7.30-7.33 (m, 1H), 7.37 (t,  $J = 7.5$  Hz, 2H), 7.44-7.46 (m, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  13.7, 14.3, 16.6, (d,  $J = 1.9$  Hz), 16.7 (d,  $J = 2.9$  Hz), 39.4, 40.3 (d,  $J = 21.9$  Hz), 103.4 (d,  $J = 186.9$  Hz), 124.5 (d,  $J = 10.5$  Hz), 128.2, 128.7 (d,  $J = 1.9$  Hz), 138.3 (d,  $J = 22$  Hz), 209.8 (d,  $J = 29.6$  Hz);  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ ):  $\delta$  -169.51 (t,  $J = 24.4$  Hz); GC/MS (EI)  $m/z$ : 203, 151, 109, 71; Anal. Calcd. for  $\text{C}_{14}\text{H}_{19}\text{FO}$ : C, 75.64; H, 8.61. Found: C, 75.93; H, 8.59.



**3-3e:** 2-fluoro-2-phenyldecan-3-one, 3-fluoro-3-phenyldecan-2-one

colorless oil, 85%, obtained as a mixture of two regioisomers in ratio of 2.2: 1. IR (neat):  $\nu$  2929, 2856, 1725, 1448, 1372, 1072, 759, 699 $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ): major isomer:  $\delta$  0.85-0.90 (m, 3H), 1.16-1.29 (m, 8H), 1.46-1.56 (m, 2H), 1.79 (d,  $J = 23$  Hz, 3H), 2.51-2.57 (m, 1H), 2.68-2.75 (m, 1H), 7.31-7.35 (m, 1H), 7.38(t,  $J = 7.5$  Hz, 2H), 7.43-7.46(m, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ): major isomer:  $\delta$  14.3, 22.8 (d,  $J = 3.8\text{Hz}$ ), 23.2 (d,  $J = 15.4\text{Hz}$ ), 29.2 (d,  $J = 10.5\text{Hz}$ ), 31.9(d,  $J = 10.5\text{Hz}$ ), 36.7, 100.9 (d,  $J = 183.1\text{Hz}$ ), 103.2(d,  $J = 186\text{Hz}$ ), 124.3(d,  $J = 9.5\text{Hz}$ ), 124.5 (d,  $J = 10.5\text{Hz}$ ), 128.4 (d,  $J = 8.6\text{Hz}$ ), 128.8(d,  $J = 8.1\text{Hz}$ ), 138.1 (d,  $J = 21.9\text{Hz}$ ), 139.4 (d,  $J = 22.9\text{Hz}$ ), 208.0(d,  $J = 31.4\text{Hz}$ ), 209.5(d,  $J = 29.6\text{Hz}$ );  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ ): major isomer:  $\delta$  -157.44 (q,  $J = 23.0\text{Hz}$ ); GC/MS (EI)  $m/z$ : 231, 165, 145, 109, 85, 57; Anal. Calcd. for  $\text{C}_{16}\text{H}_{23}\text{FO}$ : C, 76.76; H, 9.26. Found: C, 76.78; H, 9.23.

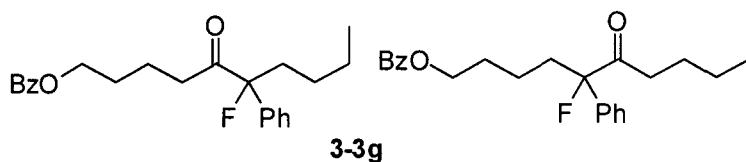


**3-3f:** 2-fluoro-2-phenylhexan-3-one, 3-fluoro-3-phenylhexan-2-one

colorless oil, 47%, obtained as a mixture of two regioisomers in ratio of 2.1: 1. IR (neat):  $\nu$  2959, 2873, 1725, 1448, 1138, 1038, 760, 699 $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,

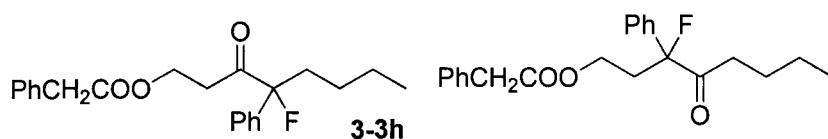


CDCl<sub>3</sub>): major isomer:  $\delta$  0.84-0.90 (m, 3H), 1.20-1.34 (m, 4H), 1.79 (d,  $J=23$ Hz, 3H), 2.51-2.58 (m, 1H), 2.69-2.76 (m, 1H), 7.32-7.35 (m, 1H), 7.39 (t,  $J = 7.5$  Hz, 2H), 7.44-7.46 (m, 2H); <sup>19</sup>F NMR (470 MHz, CDCl<sub>3</sub>): major isomer:  $\delta$  -157.38 (q,  $J = 23.0$  Hz); GC/MS (EI)  $m/z$ : 189, 165, 123, 63.



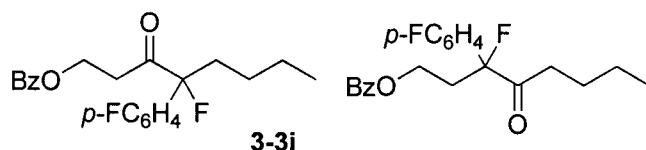
**3-3g:** 6-fluoro-5-oxo-6-phenyldecyl benzoate, 5-fluoro-6-oxo-5-phenyldecyl

colorless oil, 83%, obtained as a mixture of two regioisomers in ratio of 5: 1. IR (neat):  $\nu$  2929, 1724, 1274, 1115, 711cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>), Major isomer:  $\delta$  0.81-0.90 (m, 3H), 1.24-1.32 (m, 8H), 2.05-2.16 (m, 1H), 2.22-2.33 (m, 1H), 3.03-3.12 (m, 2H), 4.55 (t,  $J = 6.0$ Hz, 2H), 7.27-7.49 (m, 8H), 7.82(d,  $J = 8.5$ Hz, 2H); <sup>19</sup>F NMR (470 MHz, CDCl<sub>3</sub>): Major isomer:  $\delta$  -170.03 (t,  $J = 24.4$ Hz); GC/MS (EI)  $m/z$ : 257, 249, 230, 135, 113, 105, 95; Anal. Calcd. for C<sub>23</sub>H<sub>27</sub>FO<sub>3</sub>: C, 74.57; H, 7.35. Found: C, 74.67; H, 7.43.



**3-3h:** 4-fluoro-4-phenyl-1-((1-phenylvinyl)peroxy)octan-3-one, 3-fluoro-3-phenyl-1-((1-phenylvinyl)peroxy)octan-4-one

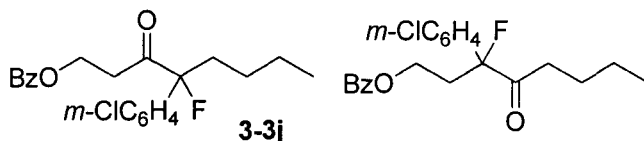
colorless oil, 70%, obtained as a mixture of two regioisomers in ratio of 5.0: 1.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ): major isomer:  $\delta$  0.89-0.92 (m, 3H), 1.20-1.37 (m, 4H), 2.08-2.17 (m, 1H), 2.20-2.30 (m, 1H), 2.87-2.94 (m, 1H), 3.00-3.06 (m, 1H), 3.50 (s, 2H), 4.29-4.38 (m, 2H), 7.21-7.46 (m, 10H);  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ ): Major isomer:  $\delta$  -169.89 (t,  $J$  = 23.9Hz); GC/MS (EI)  $m/z$ : 221, 201, 191, 165, 145, 135, 109.



**3-3i:** 4-fluoro-4-(4-fluorophenyl)-3-oxooctyl benzoate, 3-fluoro-3-(4-fluorophenyl)-4-oxooctyl benzoate

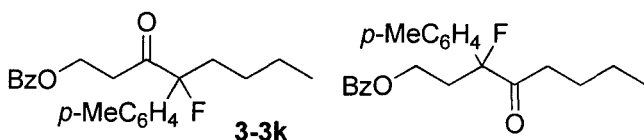
colorless oil, 88%, obtained as a mixture of two regioisomers in ratio of 5.3: 1. IR (neat):  $\nu$  2959, 1724, 1275, 1116, 835, 712  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ): major isomer:  $\delta$  0.75-1.00 (m, 3H), 1.16-1.23 (m, 4H), 1.92-2.09 (m, 1H), 2.09-2.20 (m, 1H), 2.93-3.01 (m, 2H), 4.42-4.47 (m, 2H), 6.91-6.98 (m, 2H), 7.26-7.36 (m, 4H), 7.41-7.44 (m, 1H), 7.69-7.71 (m, 2H);  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ ): Major isomer:  $\delta$  -169.27 (t,  $J$  = 24.9Hz); GC/MS (EI)  $m/z$ : 239, 219, 177, 153,

127, 105, 77; Anal. Calcd. for  $C_{21}H_{22}F_2O_3$ : C, 69.99; H, 6.15. Found: C, 70.26; H, 6.07.



**3-3j:** 4-(3-chlorophenyl)-4-fluoro-3-oxooctyl benzoate, 3-(3-chlorophenyl)-3-fluoro-4-oxooctyl benzoate

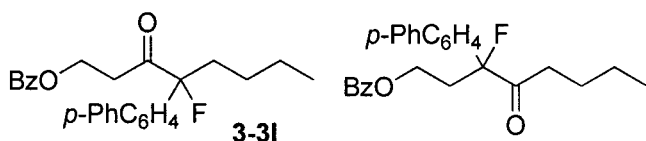
colorless oil, 71%, obtained as a mixture of two regioisomers in ratio of 3.4: 1. IR (neat):  $\nu$  2959, 1724, 1274, 1115, 712 $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ ): major isomer:  $\delta$  0.80-0.91 (m, 3H), 1.14-1.34 (m, 4H), 2.02-2.19 (m, 1H), 2.19-2.30 (m, 1H), 2.85-3.11 (m, 2H), 4.55 (t,  $J$  = 6.5Hz, 2H), 7.27-7.46 (m, 7H), 7.51-7.55(m, 1H), 7.82-7.84 (m, 1H);  $^{19}F$  NMR (470 MHz,  $CDCl_3$ ): Major isomer:  $\delta$  -169.27 (t,  $J$  = 24.9Hz); GC/MS (EI)  $m/z$ : 291, 257, 236, 189, 169, 105; Anal. Calcd. for  $C_{21}H_{22}ClFO_3$ : C, 66.93; H, 5.88. Found: C, 66.97; H, 5.85.



**3-3k:** 4-fluoro-3-oxo-4-(p-tolyl)octyl benzoate, 3-fluoro-4-oxo-3-(p-tolyl)octyl benzoate

colorless oil, 88%, obtained as a mixture of two regioisomers in ratio of 6.7: 1. IR (neat):  $\nu$  2958, 2871, 1724, 1452, 1275, 1115, 712 $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ ): major isomer:  $\delta$  0.85-0.88 (m, 3H), 1.26-1.33 (m, 4H), 2.02-2.18 (m, 1H),

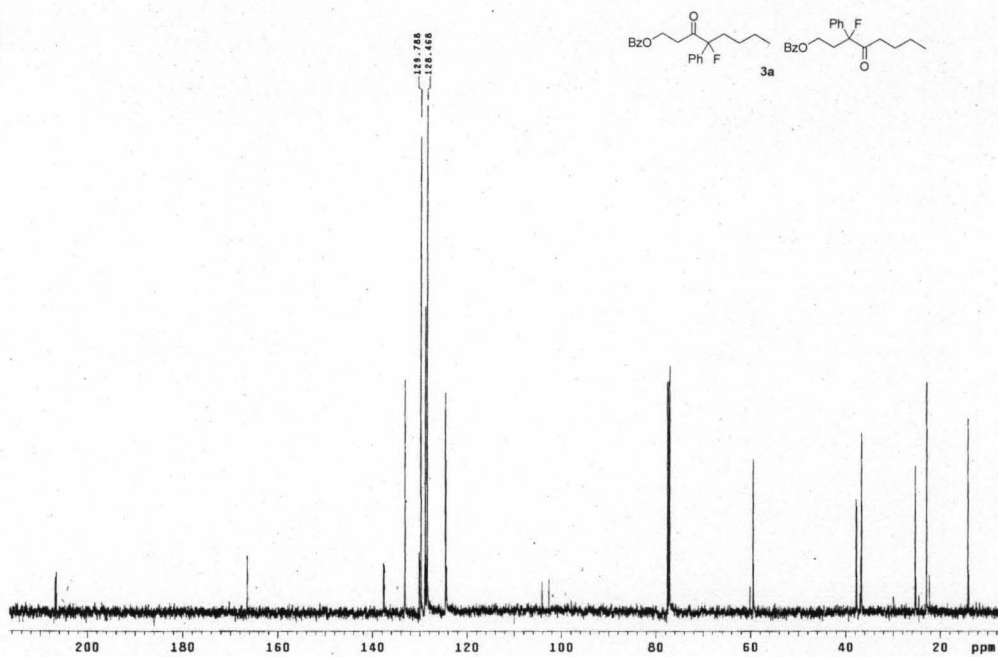
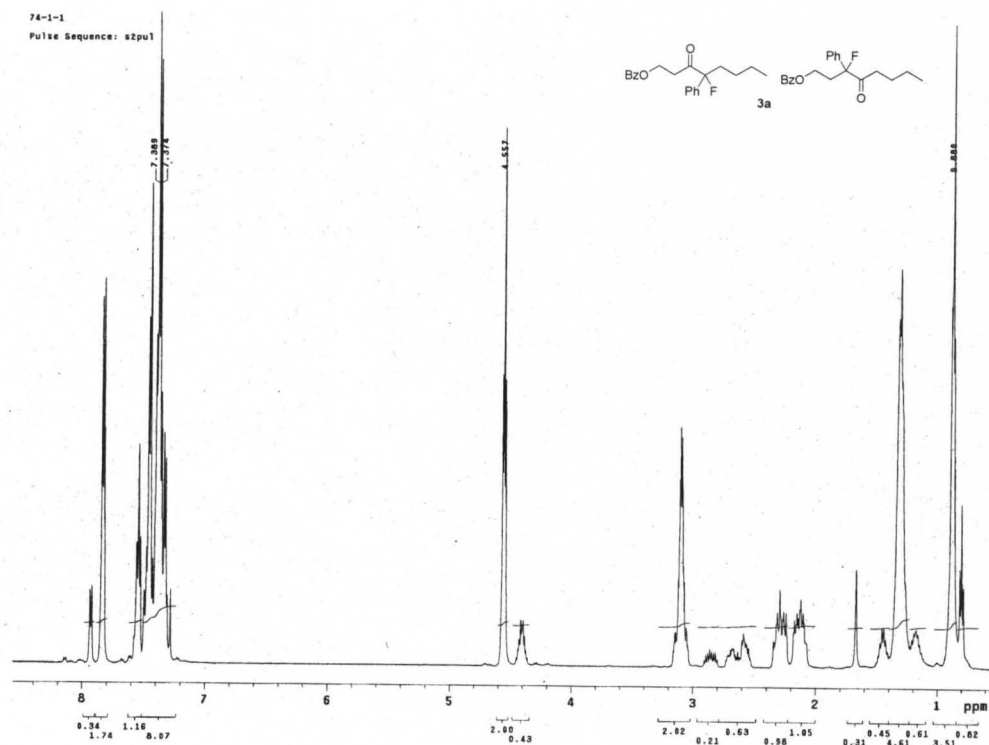
2.19-2.30 (m, 1H), 2.33(d,  $J = 4\text{Hz}$ , 3H), 3.06-3.09 (m, 2H), 4.54(t,  $J = 5.5\text{Hz}$ , 2H), 7.15-7.18 (m, 2H), 7.31-7.42 (m, 4H), 7.52-7.55(m, 1H), 7.82-7.84 (m, 2H);  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ ): major isomer:  $\delta$  -169.71 (t,  $J = 24.9\text{Hz}$ ); GC/MS (EI)  $m/z$ : 296, 277, 261, 221, 196, 185, 165, 123, 105, 77; Anal. Calcd. for  $\text{C}_{22}\text{H}_{25}\text{FO}_3$ : C, 74.13; H, 7.07. Found: C, 74.40; H, 7.08.



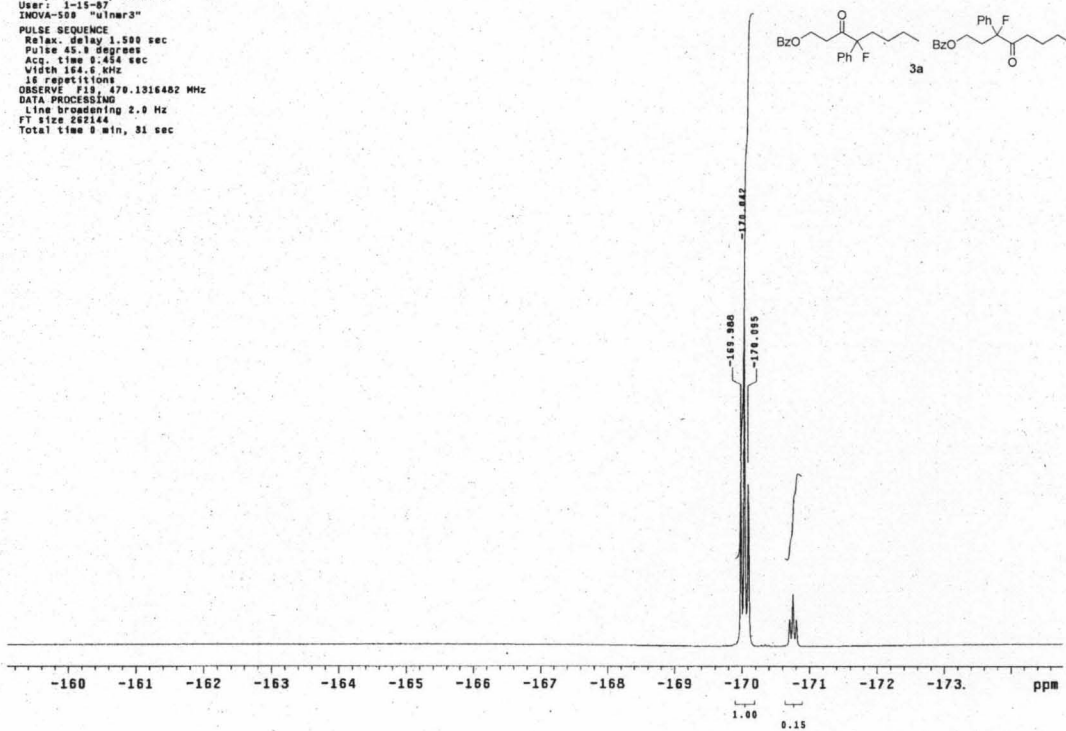
**3-3I**: 4-([1,1'-biphenyl]-4-yl)-4-fluoro-3-oxooctyl benzoate, 3-([1,1'-biphenyl]-4-yl)-3-fluoro-4-oxooctyl benzoate

colorless oil, 90%, obtained as a mixture of two regioisomers in ratio of 5.3: 1. IR (neat):  $\nu$  2958, 1723, 1487, 1275, 1115, 765, 712 $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ): major isomer:  $\delta$  0.89-1.18 (m, 3H), 1.27-1.44 (m, 4H), 2.11-2.22 (m, 1H), 2.27-2.38 (m, 1H), 3.10-3.16 (m, 2H), 4.59 (t,  $J = 6.0\text{Hz}$ , 2H), 7.31-7.63(m, 12H), 7.84-7.85(m, 2H);  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ ): major isomer:  $\delta$  -169.75 (t,  $J = 24.9\text{Hz}$ ); GC/MS (EI)  $m/z$ : 296, 277, 261, 242, 222, 199, 185, 165, 116, 90; Anal. Calcd. for  $\text{C}_{27}\text{H}_{27}\text{FO}_3$ : C, 77.49; H, 6.50. Found: C, 77.62; H, 6.57.

$^1\text{H}$ ,  $^{13}\text{C}$ ,  $^{19}\text{F}$  Spectras of compound 3-3a



Pulse Sequence: s2pul  
 Solvent: CDCl<sub>3</sub>  
 Temp: 25.9 C / 298.1 K  
 User: 1-15-07  
 INOVA-500 "ulnmr3"  
 PULSE SEQUENCE  
 Relax. delay 1.500 sec  
 Pulse 45.0 degrees  
 Acq. time 8.454 sec  
 Width 164.6 kHz  
 16 repetitions  
 OBSERVE F20, 470.1316402 MHz  
 DATA PROCESSING  
 Line broadening 2.0 Hz  
 FT size 262144  
 Total time 8 min, 31 sec



## CHAPTER 4. SYNTHESIS OF FLUOROHYDRINS FROM ALLYL SILANES

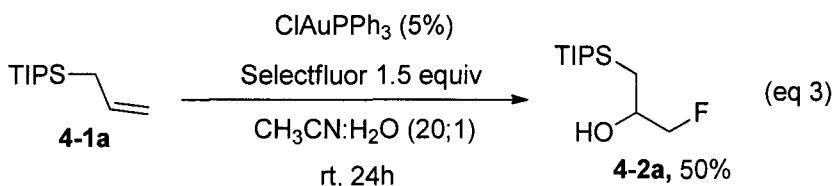
### 4.1 Background

Extensive research has established that the chemical reactivity of fluorinated organic compounds is distinctly different from other halide-containing analogues.<sup>18-24</sup> Consequently, fluorine substitution can effectively modify the physico-chemical properties of a molecule. In this regard, fluorohydrins have been sought after as intermediates and biological targets.<sup>137-145</sup> Typically, fluorohydrins are synthesized by an epoxide ring opening using a fluorinating agent,<sup>146-152</sup> but in many cases the regioselectivity and yields are less than satisfactory. There are other methods that rely on fluorinated molecular building blocks, but these building blocks are often derived from potential ozone depleting agents like  $\text{CFHCl}_2$ .<sup>153</sup>

### 4.2 Results and discussion

Selectfluor is an exceptionally stable, virtually non-hygroscopic crystalline electrophilic fluorinating agent<sup>36,37</sup> used in several applications such as fluorohydroxylation of aryl substituted allenes.<sup>154</sup> Recently, we reported a versatile synthesis of fluoroketones via a gold-catalyzed fluorination of alkynes using Selectfluor.<sup>155</sup> During our attempts to extend the scope of this reaction to

alkenes, we conducted the fluorination of allyltriisopropylsilane **4-1a** in the presence of 5% AuClPPh<sub>3</sub>; this reaction afforded the fluorohydrin product **4-2a** in around 50% yield (eq 3). Further investigations revealed that no other regioisomer formed. This reaction represented a highly regioselective intermolecular fluorohydroxylation of an alkene. Gouverneur and co-workers have reported an electrophilic fluorocyclization of allyl silanes,<sup>156</sup> but to the best of our knowledge, the synthetically more useful intermolecular fluorohydroxylation of allyl silanes has not been reported before.



Further optimization of this transformation is shown in Table 7. Without any gold catalyst, the fluorination of **4-1a** in CH<sub>3</sub>CN:H<sub>2</sub>O (20:1) gave 1-fluoro-3-(triisopropylsilyl)propan-2-ol **4-2a** (entry 1) in 56%, which indicated that the reaction occurred independently of the gold catalyst. Increasing the amount of water led to a slightly increased yield (entry 2) but further increases in water content actually decreased the yield (entry 3). We also investigated other nucleophiles. No reaction was observed when ethanol only was used as nucleophile and solvent (entry 4), but the fluorination of **4-1a** in CH<sub>3</sub>CN: C<sub>2</sub>H<sub>5</sub>OH (10:1) afforded (2-ethoxy-3-fluoropropyl) triisopropylsilane **4-2a** in 61% yield (entry 5). This result indicated that the solvent (CH<sub>3</sub>CN) played an important role in this transformation. The reaction of **4-1a** with other nucleophiles like acetic acid, formamide and diethylamine afforded complicated mixtures (entries 6-8).



Thus, the reaction condition presented in entry 2 was regarded as optimum for further studies.

**Table 7. Screening conditions for the reaction of fluorohydroxylation of allyl silanes.**

entry	Nucleophile (CH <sub>3</sub> CN:Nu)	product yield
1	H <sub>2</sub> O (20:1)	56%
2	H <sub>2</sub> O (10:1)	60%
3	H <sub>2</sub> O ( 5:1)	55%
4	C <sub>2</sub> H <sub>5</sub> OH only	no rxn
5	C <sub>2</sub> H <sub>5</sub> OH (10:1)	61%
6	CH <sub>3</sub> COOH (10:1)	complex mixture
7	HCONH <sub>2</sub> (10:1)	complex mixture
8	Et <sub>2</sub> NH ( 10:1)	no rxn

With optimized reaction conditions on hand, we explored the scope of this transformation (Table 8). The reactions of allyltriisopropylsilane **4-1a** with different nucleophiles like water, ethanol, isopropanol, allyl alcohol, butan-1-ol and 2-cyclohexylethanol gave good yields (entries 1-6,). The relative more sterically hindered isopropanol reduced the yield slightly (entry 3, Table 8). Higher temperature (60°C) was needed for the completion of the reaction of **4-1a** with allyl alcohol, furnishing product **4-2d** in 61% yield (entry 4, (Table 8). Reaction of allyltriphenylsilane **4-1b** with CH<sub>3</sub>CN:H<sub>2</sub>O (10:1) afforded **4-2g** in 55% yield (entry 7, Table 8). Diallyl silanes, like diallyldiphenylsilane **4-1c**, seemed highly reactive under the standard conditions and failed to give the

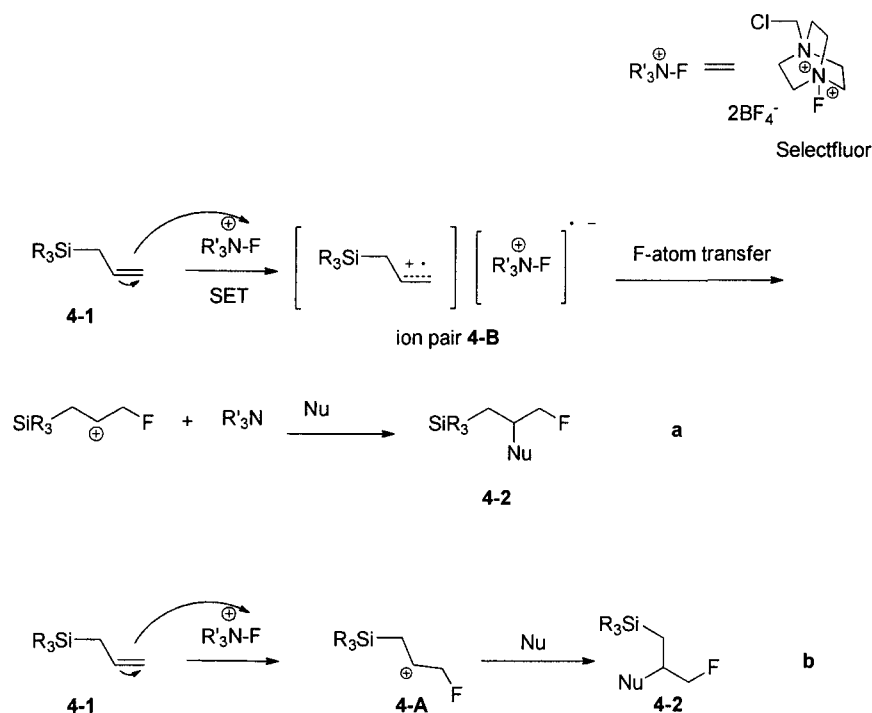
desired fluorinated product (entry 8, Table 8). The reaction of allyl silane with a non-terminal double bond like **4-1d** worked well (entry 9, Table 8). The good, but not excellent, yields observed in Table 8 may be due to a competing electrophilic fluorodesilylation reaction of allyl silane **4-1**. Gouverneur and co-workers have developed efficient syntheses of allyl or propargyl fluorides through fluorodesilylation of allyl and allenyl silanes.<sup>157-162</sup> In those transformations,<sup>157-162</sup> allyl silanes with a smaller silyl group (e.g. TMS) were used. The bulkier silyl group (e.g., TIPS) used in our examples are more resisting to fluorodesilylation, but may not completely prevent the fluorodesilylation process. If desired, the silyl group in **4-2** can be removed using literature methods.<sup>156</sup>

The proposed mechanism is shown in Scheme 26. It has been well established that the silyl group has a strong stabilization effect on  $\beta$ -carbocations or radical cations.<sup>163</sup> This fact is probably the key factor for the regioselectivity observed. We propose that allyl silane reacts with Selectfluor to give  $\beta$ -carbocation **4-A**, and quenching of **4-A** by a nucleophile to give the final product **4-2** (Scheme 26-b). Single electron transfer (SET) has been proposed in many Selectfluor-mediated reactions;<sup>36</sup> it is also possible that our reaction goes through a SET mechanism (Scheme 26-a), that is, the reaction of **4-1** with Selectfluor would give radical cation **4-B** which will undergo F-atom transfer and then react with a nucleophile to give the final product **4-2**.

**Table 8. Scope for the reaction of fluorohydroxylation of allyl silanes.**

$  \begin{array}{ccc}  \text{R}_3\text{Si}-\text{CH}_2-\text{CH}=\text{CH}_2 & \xrightarrow[\text{CH}_3\text{CN:Nu (10:1) rt, 24h-36h}]{\text{Selectfluor 1.5 equiv}} & \text{R}_3\text{Si}-\text{CH}_2-\text{CH}(\text{Nu})-\text{CH}_2\text{F} \\  \text{4-1} & & \text{4-2}  \end{array}  $			
entries	4-1	Nu	4-2, yield <sup>a</sup>
1		H <sub>2</sub> O	 <b>4-2a</b> , 60%
2	<b>4-1a</b>	C <sub>2</sub> H <sub>5</sub> OH	 <b>4-2b</b> , 61%
3	<b>4-1a</b>		 <b>4-2c</b> , 43%
4 <sup>b</sup>	<b>4-1a</b>		 <b>4-2d</b> , 61%
5	<b>4-1a</b>		 <b>4-2e</b> , 60%
6	<b>4-1a</b>		 <b>4-2f</b> , 62%
7	 <b>4-1b</b>	H <sub>2</sub> O	 <b>4-2g</b> , 55%
8	 <b>4-1c</b>	H <sub>2</sub> O	complex mixture
9	 <b>4-1d</b>	H <sub>2</sub> O	 <b>4-2h</b> , 59%

<sup>a</sup> isolated yields; <sup>b</sup> reaction was conducted at 60°C.



**Scheme 26.** Proposed mechanism for formation of compound 4-2.

### 4.3 Conclusion

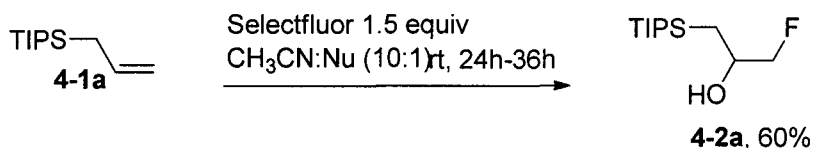
In conclusion, we have developed a convenient method for the efficient monofluorination of allyl silanes using Selectfluor as the electrophilic fluorination reagent. The stabilization effect of the silyl group on the  $\beta$ -carbocation is critical for the success of this fluorohydroxylation reaction. The use of easy-to-handle N-F reagents is a particularly attractive feature of our reaction. Further research on the implications of this transformation, including an asymmetrical version, is currently being conducted in our laboratory.

## 4.4 Experimental

### General

$^1\text{H}$ ,  $^{13}\text{C}$  and  $^{19}\text{F}$  NMR spectra were recorded at 500, 126 and 470 MHz respectively, using  $\text{CDCl}_3$  as a solvent. The chemical shifts are reported in  $\delta$  (ppm) values relative to  $\text{CHCl}_3$  (7.26 ppm for  $^1\text{H}$  NMR and 77.0 ppm for  $^{13}\text{C}$  NMR) and  $\text{CFCl}_3$  (0 ppm for  $^{19}\text{F}$  NMR), multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), m (multiplet) and br (broad). Coupling constants,  $J$ , are reported in Hertz. Coupling constants are reported in hertz (Hz). All air and/or moisture sensitive reactions were carried out under argon atmosphere. Solvents (tetrahydrofuran, ether, dichloromethane and DMF) were chemically dried using a commercial solvent purification system. All other reagents and solvents were employed without further purification. The products were purified using a CombiFlash system (Teledyne ISCO) or a regular glass column. TLC was developed on Merck silica gel 60 F254 aluminum sheets. IR spectra were recorded on a Bruker IFS 25 spectrometer. High resolution ESI-MS were obtained using a MS-FTICR-MS system (LTQ FT, Thermo Electron Corp.) at the CREAM Mass Spectrometry Facility, University of Louisville, Kentucky, 40292. When needed, reactions were monitored using  $^{19}\text{F}$  NMR and the mixture percentage yield was obtained using  $\alpha,\alpha,\alpha$ -trifluoromethylbenzene as internal reference.

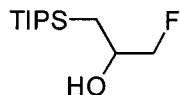
### General procedure for synthesis of compound 4-2.



To a solution of **4-1a** (99 mg, 0.5 mmol) in 3 mL of MeCN : H<sub>2</sub>O (10 : 1) was added subsequently Selectfluor (266 mg, 0.75 mmol). Then the reaction mixture was stirred at room temperature for 24-36 h; the progress of reaction was monitored by TLC. After completion of the reaction, the mixture was quenched with saturated NH<sub>4</sub>Cl solution, extracted with hexane or ether (15 mL x 2) and the combined organic layers were dried over Mg<sub>2</sub>SO<sub>4</sub>. After evaporation of organic solvents, the residue was subjected to flash silica gel column chromatography (from hexane to hexane/CH<sub>2</sub>Cl<sub>2</sub> = 1:1), affording **4-2a** as colorless oil (70 mg, 60%).

### Spectroscopic data of compounds 4-2

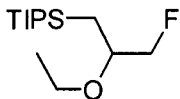
1-fluoro-3-(triisopropylsilyl)propan-2-ol (**4-2a**)



Colorless oil, yield 60%. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 0.68-0.74 (m, 1H), 0.78-0.86 (m, 1H), 1.02-1.17 (m, 21H), 2.17 (s, 1H), 4.10-4.27 (m, 2H), 4.31-4.44 (m, 1H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 11.6, 12.2 (d, *J* = 4 Hz), 19.0 (d, *J* = 2 Hz), 68.2 (d, *J* = 18 Hz), 89.2 (d, *J* = 170 Hz). <sup>19</sup>F NMR (470 MHz, CDCl<sub>3</sub>): δ -220.8 - -

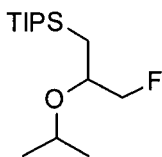
220.5 (m).GC/MS (EI)  $m/z$ : 172, 103, 41.HRMS (ESI) calcd. for  $C_{12}H_{27}FNaOSi^+$  ( $[M+Na]^+$ ) 257.1713, found 257.1712.

(2-ethoxy-3-fluoropropyl)triisopropylsilane (**4-2b**)



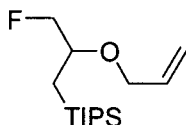
Colorless oil (yield 61%).  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  0.73-0.77 (m, 1H), 0.89-0.94 (m, 1H), 1.04-1.09 (m, 21H), 1.20 (t,  $J$  = 7 Hz, 3H), 3.47-3.53 (m, 1H), 3.71-3.78 (m, 2H), 4.29-4.36 (m, 1H), 4.39-4.46 (m, 1H).  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  11.7, 11.8 (d,  $J$  = 5 Hz), 15.9, 19.0, 65.5, 75.9 (d,  $J$  = 18 Hz), 87.9 (d,  $J$  = 174 Hz).  $^{19}F$  NMR (470 MHz,  $CDCl_3$ ):  $\delta$  -220.3 - -220.1 (m).GC/MS (EI)  $m/z$ : 243, 202, 147, 121, 41; Anal. Calcd. for  $C_{14}H_{31}FOSi$ : C, 64.06; H, 11.90.HRMS (ESI) calcd. for  $(C_{14}H_{31}FNaOSi)^+$  ( $[M+Na]^+$ ) 285.2026, found 285.2026.

(3-fluoro-2-isopropoxypropyl)triisopropylsilane (**4-2c**)



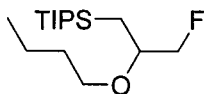
Colorless oil, yield 43%.  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  0.76-0.83 (m, 2H), 0.96-1.03 (m, 21H), 1.09 (d,  $J$  = 7.5 Hz, 6H), 3.71-3.81 (m, 2H), 4.16-4.38 (m, 2H).  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  11.5, 12.5 (d,  $J$  = 7.5 Hz), 18.8 (d,  $J$  = 5 Hz), 22.3, 23.2, 69.8 (d,  $J$  = 2 Hz), 72.8 (d,  $J$  = 22 Hz), 87.4 (d,  $J$  = 216 Hz).  $^{19}F$  NMR (470 MHz,  $CDCl_3$ ):  $\delta$  -220.4 - -220.1; GC/MS (EI)  $m/z$ : 216, 192, 172, 103.HRMS (ESI+) calcd. for  $C_{15}H_{33}FNaOSi^+$  ( $[M+Na]^+$ ) 299.2182, found 299.2184.

(2-(allyloxy)-3-fluoropropyl)triisopropylsilane (**4-2d**)



Colorless oil, yield 61%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.67-0.71 (m, 2H), 0.77-1.03(m, 21H), 3.70-3.78 (m, 1H), 3.94-3.98 (m, 1H), 4.10-4.15 (m, 1H), 4.22-4.29 (m, 1H), 4.34-4.30 (m, 1H), 5.05-5.09 (m, 1H), 5.17-5.21 (m, 1H), 5.80-5.89 (m, 1H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  11.4, 18.8, 71.0 (d,  $J = 3$  Hz), 75.6(d,  $J = 22$  Hz), 88.7 (d,  $J = 217$  Hz), 116.5, 135.1.  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ ):  $\delta$  -219.5- -219.2 (m). GC/MS (EI)  $m/z$ : 213, 189, 171, 81. HRMS (ESI) calcd. for  $\text{C}_{15}\text{H}_{31}\text{FNaOSi}^+$  ( $[\text{M}+\text{Na}]^+$ ) 297.2026, found 297.2026.

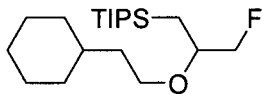
(2-butoxy-3-fluoropropyl)triisopropylsilane (**4-2e**):



Colorless oil, yield 60%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.74-0.78 (m, 2H), 0.90-0.95 (m, 3H), 1.05-1.10 (m, 21H), 1.36-1.40 (m, 2H), 1.53-1.60 (m, 2H), 3.43-3.47 (m, 1H), 3.62-3.67 (m, 1H), 3.69-3.77 (m, 1H), 4.29-4.36 (m, 1H), 4.39-4.46 (m, 1H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  11.7, 11.8, 14.1, 19.1, 19.6, 32.6, 70.0, 76.0 (d,  $J = 17$  Hz), 87.8 (d,  $J = 174$  Hz).  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ ):  $\delta$  -220.5- -220.2 (m). GC/MS (EI)  $m/z$ : 275, 231, 174, 100. HRMS (ESI $^+$ ) calcd. for  $\text{C}_{16}\text{H}_{35}\text{FNaOSi}^+$  ( $[\text{M}+\text{Na}]^+$ ) 313.2339, found 313.2339.

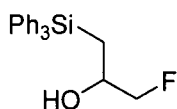


(2-(2-cyclohexylethoxy)-3-fluoropropyl) triisopropylsilane (**4-2f**):



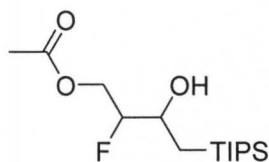
Colorless oil, 60%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.64-0.90 (m, 2H), 0.81-0.87 (m, 3H), 0.92-1.04 (m, 21H), 1.05-1.19 (m, 4H), 1.30-1.41 (m, 2H), 1.51-1.63 (m, 4H), 3.34-3.40 (m, 1H), 3.58-3.68 (m, 2H), 4.19-4.26 (m, 1H), 4.33-4.38 (m, 1H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  11.7, 11.8, 18.3, 19.1(d,  $J = 3$  Hz), 26.7(d,  $J = 37$  Hz), 33.6 (d,  $J = 23$  Hz), 34.7, 38.0, 68.1, 76.0 (d,  $J = 18$  Hz), 87.9 (d,  $J = 174$  Hz);  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ ):  $\delta$  -220.0- -219.7 (m); GC/MS (EI)  $m/z$ : 283, 214, 172, 158, 69. HRMS (ESI $^+$ ) calcd. for  $\text{C}_{20}\text{H}_{41}\text{FNaOSi}^+$  ( $[\text{M}+\text{Na}]^+$ ) 367.2808, found 367.2808.

1-fluoro-3-(triphenylsilyl)propan-2-ol (**4-2g**)



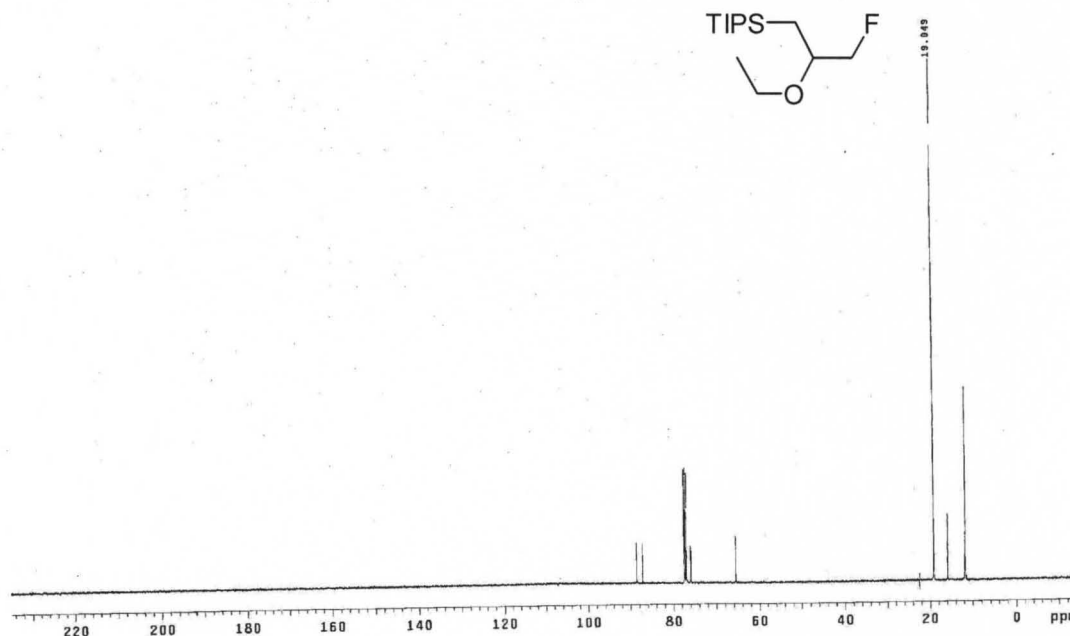
Colorless oil, yield 55%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.64-0.90 (m, 2H), 0.81-0.87 (m, 3H), 0.92-1.04 (m, 21H), 1.05-1.19 (m, 4H), 1.30-1.41 (m, 2H), 1.51-1.63 (m, 4H), 3.34-3.40 (m, 1H), 3.58-3.68 (m, 2H), 4.19-4.26 (m, 1H), 4.33-4.38 (m, 1H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  11.7, 11.8, 18.3, 19.1(d,  $J = 3$  Hz), 26.7 (d,  $J = 37$  Hz), 33.6 (d,  $J = 23$  Hz), 34.7, 38.0, 68.1, 76.0(d,  $J = 18$  Hz), 87.9 (d,  $J = 174$  Hz).  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ ):  $\delta$  -220.0 - -219.7(m). GC/MS (EI)  $m/z$ : 283, 214, 172, 158, 69

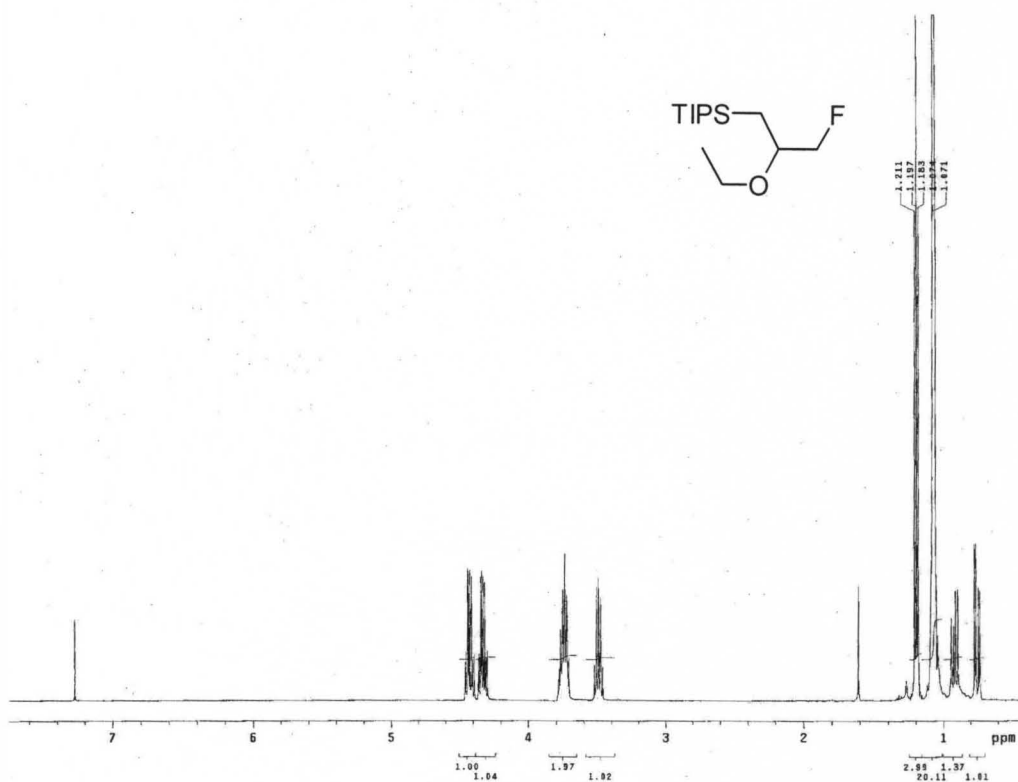
2-fluoro-3-hydroxy-4-(triisopropylsilyl)butyl acetate (**4-2h**)



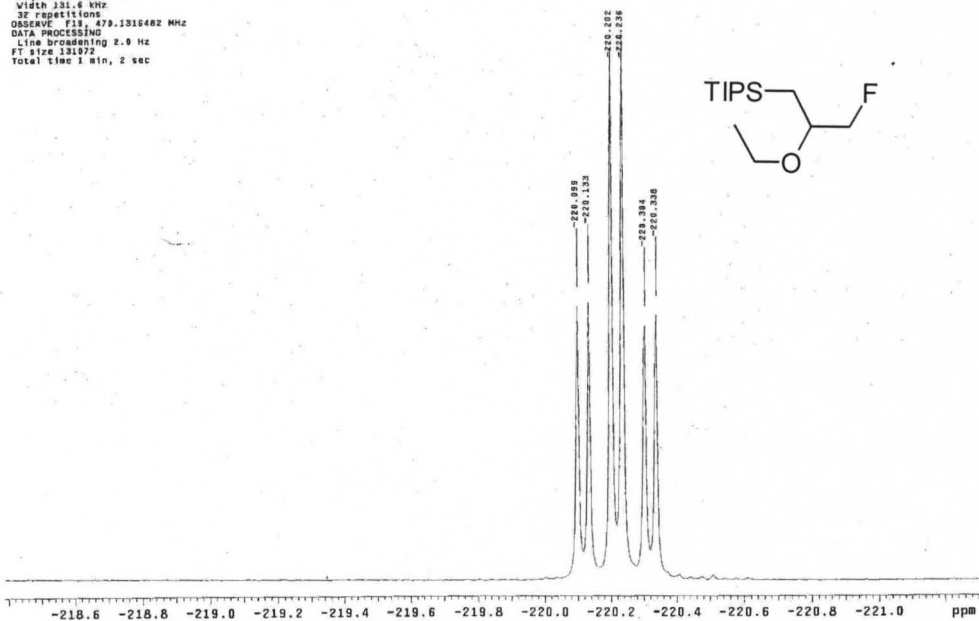
Colorless oil, yield 59%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.79-0.82 (m, 1H), 0.91-0.96 (m, 1H), 1.06-1.14 (m, 21H), 1.99 (d,  $J = 5$  Hz, 1H), 2.11-2.13 (m, 3H), 3.98-4.04 (m, 1H), 4.25-4.35 (m, 1H), 4.37-4.43 (m, 1H), 4.48-4.51 (m, 1H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  11.6 (d,  $J = 9$  Hz), 13.5, 19.0, 21.0, 63.7 (d,  $J = 23$  Hz), 68.5 (d,  $J = 20$  Hz), 95.8 (d,  $J = 175$  Hz).  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ ):  $\delta$  -198.2 - -197.9 (m). GC/MS (EI)  $m/z$ : 285, 225, 181, 112, 43. HRMS (ESI) calcd. for  $\text{C}_{15}\text{H}_{31}\text{FNaO}_3\text{Si}^+$  ( $[\text{M}+\text{Na}]^+$ ) 329.1924, found 329.1924.

$^1\text{H}$ ,  $^{13}\text{C}$ ,  $^{19}\text{F}$  spectras of compound **4-2b**





Pulse Sequence: s2pul  
 Solvent: CDCl3  
 Temp: 25.0 C / 298.1 K  
 User: 1-15-87  
 INOVA-500 "ulnar3"  
 PULSE SEQUENCE  
 Relax. delay 1.500 sec  
 Pulse 45.0 degrees  
 Acq. time 0.454 sec  
 Width 331.0 kHz  
 32 repetitions  
 OBSERVE F19, 479.1316482 MHz  
 DATA PROCESSING  
 Line broadening 2.0 Hz  
 FT size 131972  
 Total time 1 min, 2 sec



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# APPENDIX

## LIST OF ABBREVIATIONS

**CI:** Chemical Ionization

**BE:** Binding energy

**DAST:** Diethylaminosulfur trifluoride

**DCM:** Dichloromethane

**DMSO:** Dimethylsulfonyl Oxide

**ESI-MS:** Electrospray Ionization mass spectrometry

**EtOAc:** Ethyl Acetate

**GC:** Gas Liquid Chromatography

**h:** Hour

**HOAc:** Acetic acid

**HOMO:** Highest occupied molecular orbital

**HPLC:** High performance liquid chromatography

**HRMS:** High resolution mass spectroscopy

**Hz:** Hertz

**IR:** Infrared

**LDA:** Lithium diisopropylamide

**LUMO:** Lowest unoccupied molecular orbital

**M:** Molar

***m*:** meta

**mg:** milligram

**min:** minute



**mL:** milliliter  
**mmol:** millimole  
**MsOH:** Methanesulfonic acid  
**mT:** millitorr  
**m/z:** mass to charge ratio  
**NFSI:** *N*-fluorobenzenesulfonimide  
**NMR:** Nuclear magnetic resonance spectroscopy  
**o:** ortho  
**p:** para  
**ppm:** Parts per million  
**PTSA:** *p*-Toluene sulfonic acid  
**RT:** Room temperature  
**SELECTFLUOR:** 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)  
**SET:** Single electron transfer  
**TBAF:** Tetra-*n*-butylammonium fluoride  
**TBS:** *tert*-Butyldimethylsilyl  
***tert*:** tertiary  
**TIPS:** Triisopropylsilyl  
**TMS:** Trimethylsilyl  
**TfOH:** Trifluoromethanesulfonic acid  
**THF:** Tetrahydrofuran  
**TLC:** Thin layer chromatography  
**TON:** Turnover number  
**TOF:** Turnover frequency  
**XPS:** X-ray photoelectron spectroscopy

# CURRICULUM VITAE

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**Master of Science in Chemistry**, 2006-2009

**Master of Engineering in Biochemical Engineering**, 2001 - 2004

East China University of Science and Technology, Shanghai, China

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**RESEARCH EXPERIENCE:**

**On-going Project: Organic Synthesis** (2008-Present)

1. Exploration of the chemistry of extended enolates, especially alkynyl enolates.
2. Exploration of the reaction of alkynyl enolate silyl acetal with various electrophiles such as halogen, epoxide, aldehyde, imine etc.
3. Synthesis of functionalized  $\alpha,\alpha$ -disubstituted  $\beta$ -alkynyl esters from allenolates through an alkynyl enolate intermediates.
4. Gold(III) catalyzed highly regioselective hydration of internal alkynes.
5. Gold catalyzed fluorination of alkynes and alkenes.

#### **Natural Products Purification and Identification (2006-2007)**

1. Isolation and purification of several natural products from Peruvian plants such as *Himatanthus sucuuba* and *Anredera Diffusa* through various chromatographic techniques.
2. A number of new compounds have been identified by UV, IR, MS,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and 2D NMR data. Testing of their biological activities will commence in the near future.

#### **Separation and Purification of Salidroside from *Rhodiola Sachalinesis* (2001- 2004)**

1. Purification of traditional Chinese medicine salidroside (\$200,000/Kg) from *Rhodiola sachalinesis* extract (\$20/Kg) by adsorption chromatography with satisfactory yield. (The product is marketed by HuaChang polymer Co., Ltd.)
2. Thermodynamics study of adsorption chromatography for industry scale-up.

#### **Generate Yeast Strain for Fast Fermentation (2000-2001)**

Successfully generated and selected fast fermentation yeast strain which can shorten fermentation time while other quality indices (such as growth rate, sugar consumption, nitrogen consumption, diacetyl content, medium flocculation, and taste) still meet or exceed national standards.

#### **OTHER EXPERIENCE:**

##### **Teaching Assistant 2006 – Present (>500 hours)**

Department of Chemistry, University of Louisville, KY, USA

Teaching Organic Chemistry Labs (CHEM 343); Organic Chemistry recitation (CHEM 341), Analytical Chemistry Labs (CHEM 208 and CHEM 209).

1. Instructed organic related classes,
2. Demonstrated experimental and equipment setups,
3. Supervised experiments run by undergraduate students
4. Review of assignments and exams.

## **Research Assistant 2001 –2003**

Hua Chang polymer Co., Ltd, Shanghai, China

1. Calibrated and maintained lab instruments
2. Preparing files, documents and posters.

## **HIGHLIGHT:**

10 years experience in synthetic organic chemistry, biochemical engineering, and natural products research.

Hands-on experience with HPLC, GC-MS, IR, UV-Vis, 1D and 2D-NMR.

Proficient with MS Office, Chemoffice, Windows, and Scifinder etc.

Excellent communication skills, multilingual (English and Chinese).

## **AWARDS & SCHOLARSHIPS:**

Excellent league member of Department (East China University of Science and Technology, ECUST) 1999-2000

University Scholarship for Academic Excellence (ECUST) 1999-2000

Excellent Student of Department (ECUST) 1999-2000

## **PUBLICATIONS:**

- (1) Xu, B.; Wang, W.; Hammond, G. B. *Library-friendly synthesis of fluorinated ketones through functionalized hydration of alkynes and investigation of the reaction mechanism. J. Fluorine Chem.* **2011**, 132, 804-810.
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### **PRESENTATIONS:**

1. Xu, B.; Liu, L.; Wang, W.; Hammond, G. B.; "Transformative alkynylogation: Extension of the electronic effects of propargyl or allenyl substrates", The Gordon Research Conferences on Stereochemistry, July 27 - August 1, 2008; Salve Regina University, Newport, RI
2. Xu, B.; Wang, W.; Liu, L.-P.; Yang, H.; Aponte, J. C.; Hammond, G. B., *Extreme Makeover: Re-visiting vinylogy and its applications in synthesis*. 41st National Organic Chemistry Symposium, Boulder, Colorado, United States, Jun 7-11, 2009, Poster No. C5.
3. "What Lies Beyond Fluorine Substitution? New Vistas from a Synthetic Standpoint" G.B. Hammond, B. Xu, W. Wang, H. Yang. Keynote Speaker presentation, 9th International Symposium on Fluorine Chemistry and ISoFT'09, Jackson Hole, Wyoming, August 23-28, 2009. Abstract: 43.